The epidemiology of pelvic inflammatory disease diagnosed in Australia

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Abstract

Pelvic inflammatory disease (PID) is a serious reproductive health issue for women that occurs when infection ascends from the lower to the upper genital tract. Possible sequalae include infertility, ectopic pregnancy and chronic pelvic pain. The sexually transmitted infections (STIs) *Chlamydia trachomatis* (chlamydia) and *Neisseria gonorrhoeae* (gonorrhoea) are commonly implicated, however the microbial aetiology is often unknown. PID diagnosis is imprecise due to its many possible clinical features and absence of an objective reliable non-invasive diagnostic test. As PID epidemiology varies between countries and population groups due to different STI prevalence and healthcare systems, country specific estimates are critical.

This thesis aims to improve understanding of the epidemiology of PID diagnosed in Australia, particularly with reference to chlamydia infection as this is the most frequently diagnosed STI in Australia. Chapters 1 and 2 discuss the evidence and describe what is known about the aetiology and epidemiology and PID, providing the rationale for this PhD program of research.

Chapter 3 involved an analysis of data for 15,690 women aged 16-49 attending a sexual health clinic, to examine the microbial characteristics of PID. At a population level, chlamydia was the more commonly identified microbial organism, with 8.2% (95% Confidence Interval (CI) 7.7, 8.6) of women chlamydia positive, 2.8% (95%CI 2.5, 3.0) diagnosed with PID, and, the adjusted population attributable fraction (aPAF) of PID associated with chlamydia was 14.1% (95%CI 9.9, 18.0). Among a subset (n=8,839) of women, 0.3% (95%CI 0.2, 0.5) were gonorrhoea positive only, 0.2% (95%CI 0.2, 0.4) were gonorrhoea and chlamydia positive, 4.7% (95%CI 4.3, 5.2) were diagnosed with PID, and the aPAF for gonorrhoea was 1%. There was a higher odds of PID for women with gonorrhoea or chlamydia (4.4-fold vs 3-fold, respectively) compared with no infection. A sub-analysis for asymptomatic women showed that 28% of PID was associated with chlamydia but only 0.6% of asymptomatic women were diagnosed with PID.

Chapter 4 involved a separate comprehensive analysis of the same dataset as in Chapter 3, to investigate the characteristics of clinically diagnosed PID where no infection was identified (pathogen-negative PID). Among 330 women with PID who were tested for

chlamydia, gonorrhoea, *Mycoplasma genitalium* and bacterial vaginosis, 62% had no infection diagnosed. Multivariable logistic regression showed that women with pathogen-negative PID were more likely to be aged ≥30 years (Adjusted Odds Ratio (AOR) 1.7, 95%CI 1.0, 3.0) and less likely to have evidence of vaginal inflammation (AOR 0.5, 95%CI 0.3, 0.9) or report recent unprotected sex (AOR 0.6, 95%CI 0.4, 1.0) than women with pathogen-positive PID.

Chapter 5 investigated PID diagnosis characteristics and time trends at a large sexual health clinic, before and after clinical audit feedback. The study found that between 2002 and 2016, the yearly PID diagnosis rate increased from 0.8% (37/4836) to 2.9% (209/7088) and an increasing proportion of women reported any symptoms (35.7% to 56.6%) or were diagnosed with an STI or bacterial vaginosis (9.4% to 21.4%). Univariable generalised linear models showed PID rates increased after audit feedback in 2007 by 8% yearly (incidence rate ratio (IRR) 1.08, 95%CI 1.06, 1.11), but were unchanged (aIRR 1.01, 95%CI 0.98, 1.03) when patient characteristics were included in multivariable analysis. Since audit feedback, the clinic has reoriented services to increase capacity for high risk patients that appear to have had a greater impact on PID diagnosis rates than audit feedback.

Chapter 6 estimated yearly (2009-2014) population rates of PID diagnosis using hospital admissions and emergency department data from three Australian states (Victoria, New South Wales, Queensland). Zero inflated Poisson regression models were used to examine variation in rates by year, age-group and residential area. In 2014 the overall PID rate per 100,000 women aged 15-44 years, was 63.3 (95%CI 60.8, 65.9) for admissions and 97.0 (95%CI 93.9, 100.2) for emergency department presentations. Comparing 2014 with 2009, the overall PID rate in admissions did not change, but when examined by type of PID, admission rates increased for chlamydial and/or gonorrhoeal PID (aIRR 1.73, 95%CI 1.31, 2.28) and unspecified PID (aIRR 1.09, 95%CI 1.00, 1.19) but declined for chronic PID (aIRR 0.83, 95%CI 0.73, 0.95). PID rates in emergency departments were higher (aIRR 1.34, 95%CI 1.24, 1.45) in 2014 than 2009 and substantially higher for women aged 15-24 (aIRR 2.78, 95%CI 2.62, 2.94) than 35-44 years.

In conclusion, this thesis provided the first Australian estimates of the population level risk of PID associated with chlamydia and gonorrhoea. This new information based on the PAF suggests that eliminating chlamydia in a high prevalence population might only reduce PID by 14% and around 1% if gonorrhoea were eliminated. For low chlamydia prevalence populations, the PAF findings suggest that only a small number of PID cases might be avoided by widespread chlamydia screening. This thesis provided updated evidence for the frequency of PID pathogens in Australia, and, the many cases without an identified pathogen highlighted the need for non-invasive bio-markers for upper genital tract inflammation. In the absence of bio-markers the decision to commence PID treatment should continue to be based on clinical features and sexual risk. This thesis found that PID remains a substantial cause of attendances at sexual health clinics and hospitalisations for reproductive related health issues for women in Australia. Analyses of sexual health clinic data demonstrated the importance of adjustment for patient characteristics in interpreting time trends, and, investigation of hospital data showed how ecological analyses of data from health settings where women with PID are managed can be used to measure PID trends. Evidence was provided for an increase in PID diagnosed in Australian emergency departments that could reflect increasing PID incidence, shifting healthcare usage from primary care, or, inadequacies in PID diagnosis and management in primary care. Primary care data and systems to monitor PID incidence are needed to better understand PID epidemiology, healthcare usage, and the impact of chlamydia and STI control policies.

Declaration

This is to certify that:

I. This thesis comprises only my original work towards the Doctor of Philosophy except where indicated in the Preface;
II. Due acknowledgment has been made in the text to all other material used; and
III. The thesis is less than 100,000 words in length, exclusive of tables, maps, bibliographies and appendices.

Signed

Jane Louise Goller 14th December 2018

Preface

This thesis is comprised of three quantitative analyses of routinely collected data from Melbourne Sexual Health Centre (MSHC) and one quantitative analysis of routinely collected hospital data to examine:

1. The population attributable fraction (PAF) of PID associated with a current chlamydia or gonorrhoea infection;
2. The characteristics of PID cases where chlamydia, gonorrhoea, *M. genitalium* or bacterial vaginosis were not detected (pathogen negative PID);
3. PID diagnosis trends over time in a sexual health clinic before and after clinical audit feedback;
4. Yearly population rates of PID diagnosis in hospital admissions and emergency department presentations across the Australian states of Victoria, New South Wales and Queensland. Ectopic pregnancy rates are also examined.

Contributions of the candidate

The candidate, Jane Louise Goller was responsible for the following:

- **Analyses of MSHC data** - Preparation of ethics submissions, all data cleaning and analysis, drafting and finalising three manuscripts that present findings for three separate studies analysing these data.
- **Analyses of hospital data -** Preparation of amendments for ethics submissions, liaison with State Departments of Health and Australian Bureau of Statistics for receipt and verification of hospital and population data, and, collation of publicly available Australian Institute of Health and Welfare data for live birth denominators. Data management, synthesis, cleaning and all analyses. Drafting and finalising the manuscript.

Contributions of others

- **Analyses of MSHC data** – Professor/s Jane Hocking (University of Melbourne) and Rebecca Guy (Kirby Institute) provided guidance on design of the three studies analysing MSHC data, the analytical methods and interpretation of

findings. Professor/s Christopher Fairley, Marcus Chen and Assoc Professor Catriona Bradshaw (MSHC) provided guidance on PID diagnosis, STI testing, MSHC processes and protocols, the electronic medical record, study design and interpretation of findings. Professor Julie Simpson (University of Melbourne) provided analytical guidance for the PAF analysis. Dr Alysha De Livera (University of Melbourne) provided analytical guidance for: a) estimating the PAF and conducting multiple imputation for missing data; b) assessment of the characteristics of pathogen negative PID cases; and, c) assessment of PID diagnosis characteristics and time trends before and after clinical audit feedback.

- **Analyses of hospital data** - Professor/s Jane Hocking (University of Melbourne), Rebecca Guy, Basil Donovan, Mathew Law, and John Kaldor (Kirby Institute), Nicola Low (University of Bern) designed and oversaw the Australian Chlamydia Control Effectiveness Pilot for which the hospital data were collected. Dr Fabian Kong (University of Melbourne) prepared the documentation for ethics submission and approvals for data collection from relevant state Departments of Health. Dr Alysha De Livera (University of Melbourne) and Professor Mathew Law (Kirby Institute) provided analytical guidance for the assessment of time trends in yearly rates of PID and ectopic pregnancy diagnosis in hospital data.

Third party editorial assistance

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Primary publications related to this PhD

Goller JL, De Livera AM, Fairley CK, Guy RJ, Bradshaw CS, Chen MY, Simpson JA, Hocking JS. Population attributable fraction of pelvic inflammatory disease associated with chlamydia and gonorrhoea: a cross-sectional analysis of Australian sexual health clinic data. Published by *Sexually Transmitted Infections* 2016 92(7):525-531. doi:10.1136/sextrans-2015-052195

Goller JL, De Livera AM, Fairley CK, Guy RJ, Bradshaw CS, Chen MY, Hocking JS. Characteristics of pelvic inflammatory disease where no sexually transmitted infection is identified: a cross-sectional analysis of routinely collected sexual health clinic data. Published by *Sexually Transmitted Infections,* 2017 93(1):68-70. doi:10.1136/sextrans-2016-052553

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Goller JL, De Livera AM, Guy RJ, Low N, Donovan B, Law M, Kaldor K, Fairley CK, Hocking JS. Rates of pelvic inflammatory disease and ectopic pregnancy in Australia, 2009-2014: ecological analysis of hospital data. Published by *Sexually Transmitted Infections*. 2018: 94:534–41. doi:10.1136/sextrans-2017-053423.

Other publications

Hocking JS, **Goller JL,** Lim MSC. A verbal invitation and specimen collection on the spot are crucial to maximise STI testing uptake in non-traditional settings. *Sexual Health*, 2015

Ward J, **Goller JL**, Ali H, Bowring A, Couzos S, Saunders M, Yau P, Kaldor J, Hellard MA. Guy RJ, Donovan B. Chlamydia among Australian Aboriginal and/or Torres Strait Islander people attending sexual health services, general practices and Aboriginal community controlled health services. *BMC Health Services Research* 2014, 14:285

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Goller JL, Fairley CK, De Livera AM, et al. Increasing sensitivity to clinical diagnosis of pelvic inflammatory disease among sexual health clinic doctors: 2002-2016. Australasian Sexual Health Conference, Canberra, Australia. 2017. (Poster)

Goller JL, De Livera AM, Guy RJ, et al. rates of pelvic inflammatory disease and ectopic pregnancy are no longer declining: an ecological analysis of Australian hospital admissions and emergency presentation data, 2009-2014. Australasian Sexual Health Conference, Canberra, Australia. 2017. (Oral presentation)

Goller JL, Fairley CK, De Livera AM, et al. Increasing sensitivity to clinical diagnosis of pelvic inflammatory disease among sexual health clinic doctors: 2002-2016. Sexrurality Conference, Lancefield. 2017. (Oral presentation)

Goller JL, De Livera AM, Guy RJ, et al. rates of pelvic inflammatory disease and ectopic pregnancy are no longer declining: an ecological analysis of Australian hospital admissions and emergency presentation data, 2009-2014. Sexrurality Conference, Lancefield, Australia. 2017. (Oral presentation)

Goller JL, De Livera AM, Guy, RJ, et al. Australian hospital admission rates of sti-related-morbidity vary by geographical area and measures of socio-economic-disadvantage, 2009-2014; World Congress on Public Health, Melbourne, Australia. 2017. (Oral presentation)

Goller JL, De Livera AM, Guy RJ, et al. Rates of pelvic inflammatory disease and ectopic pregnancy are no longer declining: An ecological analysis of Australian hospital admissions and emergency presentation data, 2009-2014. STI & HIV World Congress, Rio de Janeiro, Brazil. 2017. (Poster)

Goller JL, De Livera AM, Guy RJ, et al. Rates of pelvic inflammatory disease and ectopic pregnancy diagnosed in Australian hospital settings, 2009-2014: an ecological analysis. Australian chlamydia conference; Sydney, Australia. 2017. (Oral presentation)

Goller JL, Fairley CK, De Livera AM, et al. Risk of pelvic inflammatory disease associated with chlamydia and gonorrhoea infection among Australian sexual health clinic attendees; Eighth meeting of the European Society for Chlamydia Research; Oxford, United Kingdom. 2016. (Poster)

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Goller JL, De Livera AM, Guy R, et al. Regional variation in emergency department presentation rates of chlamydia related morbidity in four states of Australia. World STI & HIV Congress; Brisbane, Australia. 2015. (Poster)

Vaisey A, **Goller JL,** Yeung A, et al. Is knowledge power? Associations between chlamydia knowledge and sexual practices in young Australian adults: findings from the Australian chlamydia control effectiveness pilot (ACCEPt). World STI & HIV Congress; Brisbane, Australia. 2015. (Poster)

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Abbreviations

ACCEPt	Australian Chlamydia Control Effectiveness Pilot
aIRR	Adjusted incidence rate ratio
AOR	Adjusted odds ratio
aPAF	Adjusted population attributable fraction
aRR	Adjusted risk ratio
CDC	Centers for Disease Control
CST	Community state type
GP	General practitioner
ICD	International Classification of Diseases
IRR	Incidence rate ratio
IUD	Intra-uterine device
MSHC	Melbourne Sexual Health Centre
MSM	Men who have sex with men
NAAT	Nucleic acid amplification test
NGU	Non-gonococcal urethritis
NSW	New South Wales
MRI	Magnetic resonance imaging
OR	Odds ratio
PAF	Population attributable fraction
PCR	Polymerase chain reaction
PEACH	Pelvic inflammatory disease Evaluation and Clinical Health study
PID	Pelvic inflammatory disease
POPI	Prevention of Pelvic Infection study
STI	Sexually transmitted infection
UK	United Kingdom
USA	United States of America

Chapter 1: Introduction

1.1 Background

1.1.1 Pelvic inflammatory disease and its epidemiology- an overview

Pelvic inflammatory disease (PID) is a clinical condition involving inflammation of the structures of the female upper genital tract. PID generally occurs as an acute infection of less than 30 days duration that follows ascension of micro-organisms from the vagina or cervix.[1-4] PID is a serious reproductive health issue for women, that can cause inflammation and scarring of the fallopian tubes that can lead to tubal factor infertility, ectopic pregnancy, or chronic pelvic pain.[4-6]

The sexually transmitted infections (STIs) *Chlamydia trachomatis* (chlamydia) and *Neisseria gonorrhoea*e (gonorrhoea)[7] are long established causes of PID. Other pathogens that have been associated with PID include *Mycoplasma genitalium,*[8 9] bacterial vaginosis,[10] *Trichomonas Vaginalis*,[11] and enteric and respiratory pathogens.[2] Another physiological pathway for developing PID has been observed when *Mycobacterium tuberculosis* or actinomyces species have infected the pelvis via the lymphatic system or blood.[2]

The clinical picture of acute PID (referring to ascending infection of recent onset) varies widely. Acute PID can be mild to moderate in severity, the key feature being bilateral recent onset lower abdominal or pelvic pain that can be accompanied by abnormal vaginal discharge, intermenstrual bleeding or dyspareunia.[2 6 12] Severe PID involves a systemic response with features such as fever, nausea and vomiting or severe pain and abdominal guarding related to peritonitis.[6 12] Some women experience no signs or symptoms as infection ascends to the upper genital tract to cause sub-clinical PID.[2 6] Depending on severity, diagnosis and management of acute PID can occur in ambulatory or inpatient settings.[12 13] The term PID is also used to refer to chronic upper genital tract inflammation, that is classified in hospital admissions as chronic salpingitis and oophoritis, or, chronic inflammatory diseases of the uterus. In hospital data, PID is also frequently classified as PID of unspecified duration.[14 15] The definition of PID for this thesis is provided in Box 1.

Box 1: Definition of PID for this thesis

The term PID in this thesis, will refer to upper genital tract inflammation arising from ascending infection from the lower genital tract. Sub-clinical PID is encompassed by this definition. However, this thesis will analyse routinely collected data sources in which a PID diagnosis is based on the clinical presentation and assessment, therefore sub-clinical PID cases are unlikely to be identified in these data. This thesis will analyse data from two routinely collected sources (sexual health clinic attendances and hospitalisations). The term PID in this thesis will also refer to unspecified PID or chronic PID that is often represented in hospital data sources.

For women with PID, timely diagnosis and effective antimicrobial management is important to reduce the risk of progression to infertility or other sequelae. Most PID diagnoses are clinically made and with a wide range of possible manifestations it is difficult to diagnose.(6, 13, 14) There is no objective, non-invasive diagnostic test or combination of signs and symptoms that are both sensitive and specific to a PID diagnosis.[6 12] Diagnostic certainty (i.e. specificity) is greater when a number of clinical features are combined to reach a PID diagnosis but comes at the expense of sensitivity thereby reducing the number of women with PID who are identified.[13 16] In order to minimise the number of PID cases that are missed, guidelines recommend a low threshold for initiating PID treatment, the minimum diagnostic criteria being any one of uterine, cervical motion or adnexal tenderness in sexually active women with recent onset pelvic pain where no other cause is identified.[13]

Due to its often poly-microbial nature, PID is treated with antibiotics to cover the likely pathogens. However, the proportion of PID cases caused by pathogens, for example *Chlamydia trachomatis* will depend on the underlying prevalence that will vary between risk groups, geographic areas and health settings. Past studies have reported detection of chlamydia in 14% to 65% of laparoscopically diagnosed PID in a range of health settings and countries[4] and gonorrhoea in 14% of laparoscopically diagnosed PID in the United Kingdom (UK).[17] Many studies of PID aetiology have been hampered by small sample size. More recently, gonorrhoea and chlamydia were detected in 4.4% and 10% respectively of women with clinically diagnosed PID in emergency departments in the United States of America (US).[18] Up to two thirds of PID cases may have no aetiological agent detected.[19]

PID and its sequelae account for substantial health care costs[20] and their prevention is an important reason for STI control policies.[21 22] Many high-income countries have introduced programs for opportunistic chlamydia testing[23 24] and the UK has implemented systematic chlamydia screening for young sexually active persons.[25] In consideration that outcomes such as infertility may not be recognised until affected women try to conceive, PID has been used as an interim outcome for monitoring the relationship between STIs and more distant adverse outcomes.[22]

At an individual level, the risk factors for PID are largely those for STI acquisition; younger age, multiple sexual partners, recent partner change, inconsistent use of barrier contraception, and a history of an STI or a repeat STI infection.[19 26] Other risks include uterine instrumentation such as for intra-uterine device (IUD) insertion, although this risk is greatest if an STI is present at the time of the procedure.[27] Availability of health care for timely STI diagnosis and management could contribute to decreased risk of PID.[28]

Measuring the distribution, determinants and outcomes of PID is challenging. These challenges stem from the fact that PID diagnosis is inaccurate, the microbial aetiology of many cases is unknown, [19] and, depending on clinical severity, women with PID will be represented in data from a range of health settings for which the terminology for a PID diagnosis is variable.[1 6 29-32] Further, few countries have PID surveillance systems, and, measurement of PID trends relies largely on ecological analyses of routinely collected data from health settings where PID is diagnosed.

1.1.2 Australian context and rationale

In Australia, chlamydia is the most commonly notified STI, around 100,000 cases in 2017, and is predominantly diagnosed among young heterosexuals.[33-35] Gonorrhoea occurs predominantly among men who have sex with men (MSM) and heterosexuals in remote Aboriginal communities, but notification rates in women more than doubled from 2007-2017 (7282 cases in women in 2017).[33-35] Care for most STIs and complications is provided through primary healthcare services that include general practice (Australia's mainstream primary care setting), Aboriginal community controlled health services, family planning and specialist sexual health clinics.[21]

Australian STI control policy has a strong focus on opportunistic chlamydia testing with objectives to detect and treat asymptomatic infections, reduce transmission and associated morbidities, including PID.[21 36] Annual or more frequent testing for chlamydia and other STIs is recommended for some priority populations, particularly among MSM.[21 37 38]

It is essential that we have data to monitor progress against STI policies and to inform future policies and programs. PID has been used as an outcome measure in chlamydia screening trials internationally,[25 39] but there are limited Australian and international data quantifying how much PID could be avoided by preventing chlamydia. Country and population group specific estimates of PID are critical to reflect the underlying prevalence of STIs and other risk factors, and, accessibility and quality of sexual health care. Aside from two data linkage studies showing the risk of PID hospitalisation was substantially higher after gonorrhoea than chlamydia infection and also higher following gonorrhoea or chlamydia compared with no infection,[40 41] there are no Australian primary care data on PID risk associated with specific pathogens. Further there is no routine surveillance for PID in Australia. Between 1992 and 2007, a number of studies showed declining PID hospital admission rates in Australia[14 24] that paralleled a general downward trend observed in many high-income countries.[24 42 43] However more recent data for Australia are needed.

The challenges in clinically diagnosing PID have been extensively documented[13 16] with variability in PID diagnosis between clinicians reported in an Australian and a UK sexual health clinic.[44 45] In the USA, some interventions to improve PID diagnosis[46 47] have been modestly successful if multifaceted (education, posters of guidelines, written discharge handouts) and targeted a range of groups, medical and nursing staff and patients. Aside from clinical audits of PID diagnosis in a sexual health clinic[44] and in Aboriginal medical services,[48] there has been limited assessment of PID diagnosis practices in Australia.

This PhD will contribute to addressing these gaps in knowledge and generate new and updated information about the epidemiology of PID diagnosed in Australia. Sexual health clinic data will form the basis for quantitative assessments of the microbial characteristics of PID diagnosed in Australia, and, investigation of PID diagnosis characteristics and time trends in the period before and after PID clinical audit feedback. Quantitative analyses of routinely collected Australian hospital data will be conducted to determine updated time trends in

rates of PID admissions. Inclusion of emergency department data in time trend analyses, will provide new information about PID epidemiology for Australia.

1.2 Aim of this thesis

This PhD seeks to improve understanding of the epidemiology of PID diagnosed in Australia, particularly with reference to chlamydia infection.

1.3 Objectives of this thesis

1. To investigate the microbial organisms associated with PID diagnosed in Australian sexual health clinic attendees
2. To investigate time trends in PID diagnosis in an Australian sexual health clinic
3. To estimate time trends in PID diagnosis in Australian hospitals

1.4 Outline of this thesis

The research undertaken in this thesis seeks to improve our understanding about the epidemiology of PID diagnosed in Australia, particularly with reference to chlamydia infection, as this is the most frequently diagnosed STI in Australia. ***The term PID (Box 1, p2) in this thesis refers to acute (mild to moderate, or severe) PID arising from ascending infection from the lower genital tract and to chronic and unspecified PID that is often represented in hospital admissions data.*** **Chapter 2** provides a detailed literature review of the aetiology and epidemiology of PID in Australia and internationally. In **Chapter 3**, the population attributable fraction (PAF) of PID associated with a current chlamydia or gonorrhoea infection was assessed among over 15 000 sexual health clinic attendees. The results were published in the journal *Sexually Transmitted Infections* in 2016 and provide new information about how much PID might be avoided by eliminating these infections. In **Chapter 4,** these sexual health clinic data were further analysed to compare the characteristics of PID cases for which chlamydia, gonorrhoea, *M. genitalium* or bacterial vaginosis were not detected (pathogen negative PID) to PID with a pathogen identified. The results were published in the journal *Sexually Transmitted Infections* in 2017. **Chapter 5** focuses on PID diagnosis by sexual health clinic doctors. PID diagnosis characteristics and trends over time before and after clinical audit feedback are investigated. A manuscript has been prepared and submitted to the journal

Sexual Health and is currently under review. This is the first study to assess time trends in PID diagnosis in an Australia sexual health clinic. In **Chapter 6**, population rates of PID diagnosis in hospital admissions and emergency presentation data across three Australian states (Victoria, New South Wales (NSW), Queensland) are presented by year for the period 2009 to 2014. Ectopic pregnancy rates using population and live birth denominators are also presented. The results were published in *Sexually Transmitted Infections* in 2018. **Chapters 3 to 6** also describe the strengths and limitation of using routinely collected data and adopt statistical approaches that consider potential biases associated with these data. **Chapter 7** discusses the Chapter findings against the objectives and the challenges faced within this PhD topic including PID aetiology and clinical diagnosis, issues related to availability of data to investigate PID epidemiology, and analytical challenges associated with routinely collected data. Implications for clinical practice, STI control, and future research are presented.

Chapter 2: Literature review

2.1 Pelvic inflammatory disease

2.1.1 Definition of pelvic inflammatory disease

The term PID encompasses a spectrum of inflammatory disorders of the female upper genital tract (endometrium, fallopian tubes, ovaries, pelvic peritoneum). PID generally occurs as an acute infection of less than 30 days duration that ascends from the lower genital tract through the cervix to cause endometritis (infection and inflammation of the uterine lining) that then spreads to the fallopian tubes to cause salpingitis (Figure **1**).[1-4 12] The terms endometritis and salpingitis have been used to refer to PID. PID is a serious reproductive health issue for women, that can cause inflammation and scarring of the fallopian tubes that in turn can lead to tubal factor infertility, ectopic pregnancy or chronic pelvic pain.[4-6] Another physiological pathway that has been observed for PID is when *Mycobacterium tuberculosis* or actinomyces species have infected the pelvis via the lymphatic system or blood.[2]

As noted in Section 1.1.1, the clinical picture of acute PID varies and can include sub-clinical PID, mild to moderate PID, and severe PID.[2 6 12] Depending on severity, diagnosis and management of acute PID can occur in ambulatory or inpatient settings.[12 13] The term PID is also used to refer to chronic upper genital tract inflammation, that is classified in hospital admissions as chronic salpingitis and oophoritis or chronic inflammatory diseases of the uterus. In hospital data, PID is also frequently classified as PID of unspecified duration.[14 15] ***The term PID (Box 1, p2) in this thesis will refer to acute (mild to moderate, or severe) PID arising from ascending infection from the lower genital tract and to chronic and unspecified PID that is often represented in hospital admissions data.***

The majority of PID cases are thought to be caused by STIs that have ascended from the vagina or cervix,[1 2] and include chlamydia, gonorrhoea,[7] and *M. genitalium.*[8 9] PID can be polymicrobial[49] and associations between bacterial vaginosis[10] and a range of enteric and respiratory pathogens have been shown.[1 2 50]

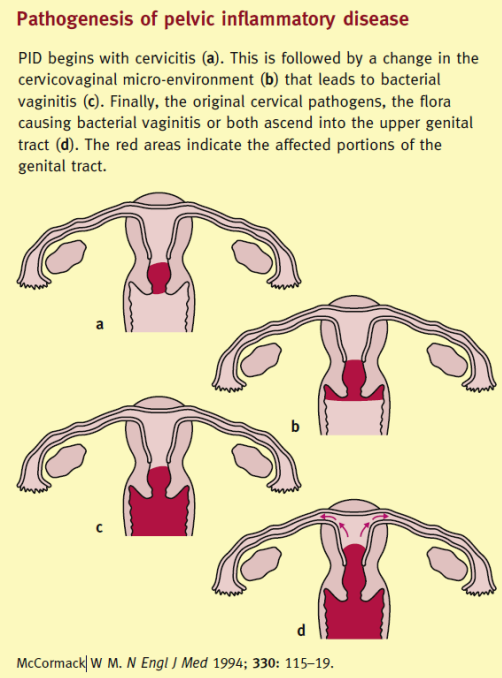

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Figure 1 Pathogenesis of pelvic inflammatory disease

2.1.2 Aetiology of pelvic inflammatory disease

The aetiology of PID is complex. A relationship between gonorrhoea, PID and infertility was recognised in the late 19th century.[7 51] Tubo-ovarian abscess and tubal obstruction were common during the gonorrhoea epidemics in the 1960s to 1980s.[52] Much of our knowledge about PID aetiology stems from epidemiological, clinical, laboratory and experimental studies conducted in the latter half of the twentieth century.[1] Laparoscopy based studies during the 1970s to 1990s enabled diagnosis of salpingitis via visualisation of erythema, oedema or exudate of the fallopian tubes in women with suspected PID and facilitated understanding of PID pathogens.[7] Although sample sizes for some studies were small, these laparoscopically based studies, showed that clinical diagnosis of PID is imprecise, with only around two-thirds of women with clinically diagnosed PID had evidence of salpingitis on laparoscopy.[7] PID research during this period highlighted the poly-microbial nature of PID with isolation of gonorrhoea, chlamydia and anaerobic micro-organisms from the fallopian tubes of women with salpingitis.[53] The term silent PID or silent salpingitis was coined to apply to the tubal damage experienced by many women but without the clinical symptoms of PID. Tubal biopsy specimens for infertile women with a history of PID and for infertile women without a history of PID have shown similar morphologic damage including flattened mucosa and reduced

ciliary beat frequency that for both groups was strongly associated with evidence of past chlamydia infection.[54] The mechanism for ascent of pathogens to the upper genital tract is still not entirely understood. It occurs via canalicular spread of pathogens from the lower genital tract to the upper genital tract.[1 55] There are a range of factors that may facilitate or hinder pathogen ascent to the upper genital tract including the vaginal microbiome, vaginal pH, cervical mucous, female sexual hormones, the endocervical epithelium, cervical ectopy, and other factors. [56-61] For younger women, many of these factors combine to create a higher risk of PID.[28] These factors in pathogen ascent are described in more detail below.

The vaginal microbiome and vaginal pH

The normal healthy vaginal microbiome comprises a mix of microorganisms that changes through a woman's lifetime. For women of reproductive age, *Lactobacillus* sp., predominate and have long been recognised as playing a protective role against infection ascent to the upper genital tract. *Lactobacillus* sp. produce lactic acid that helps to maintain vaginal pH at or below 4.5, thereby inhibiting growth of non-indigenous aerobic and anaerobic organisms and subsequent ascending infection.[56] This healthy mix of vaginal flora is susceptible to many influences. If disrupted it can result in an elevated pH and bacterial vaginosis that is characterised by an overgrowth of anaerobes or other microbes[57] and increased risk of chlamydia and gonorrhoea infection[58] and subsequent ascent of micro-organisms to the upper genital tract.

During the 21st century molecular based techniques have been increasingly used to study the human microbiome in health and disease, including the female reproductive tract.[62-64] These studies have facilitated a deeper understanding of the complexity of the vaginal microbiota and the associated risk of urogenital infection. For asymptomatic reproductive age women, five main bacterial communities or community state types (CSTs) of the healthy vaginal microbiota have been identified. Four are dominated by *Lactobacillus* sp., *L. iners* (CST I), *L. crispatus* (CST II), *L. gasseri* (CST III), *L. jenseni* (CST V), and, the fifth (CST IV) has lower proportions of *Lactobacillus* sp., higher vaginal pH, and higher proportions of anaerobic organisms including bacterial vaginosis associated bacteria. Vaginal pH and the proportions of each CST have also been found to vary between different ethnic groups.[65 66]

The composition of some bacterial communities can vary markedly over time. Factors associated with instability include menstruation, pregnancy and sexual activity but are poorly understood. *L. crispatus*, and *L. gasseri* dominated communities seem the most consistent, with transitions to another CST largely associated with menstruation before reverting to the usual CST.[67] *L. Iners* dominated and low *Lactobacillus* sp. communities are less stable, with transitions from *L. iners* to a low *Lactobacillus* sp. community observed.[67] Importantly, women with low vaginal *Lactobacillus* sp. whilst often asymptomatic for bacterial vaginosis are at risk of urogenital infections.[68] Associations for chlamydia infection with both *L. iners* dominated and low *Lactobacillus* sp. communities have been reported[69] and in-vitro studies of cervical epithelial cells have shown that different types of lactic acid from *Lactobacillus* sp. are associated with protection against chlamydia infection that is dependent on pH level.[70] In general, it appears that more diverse vaginal microbiota are less resilient to disturbance and at increased risk of disease.[69]

Cervical mucous and female sexual hormones

The cervix acts as a natural barrier to pathogens entering the endometrial cavity via downward flow of mucous and the cervical mucous plug. During the menstrual cycle the cervical mucous varies in viscosity depending on the phase of the cycle.[59 60] In the follicular phase (beginning the first day of menstrual bleeding), oestrogen production increases until oestrogen levels are highest around two weeks later when ovulation occurs (the ovulatory phase).[71] As oestrogen levels increase, the cervical mucous decreases in viscosity and becomes watery to facilitate movement of spermatozoa. Following ovulation, is the luteal phase that ends just before menstruation, unless fertilisation occurs. During the luteal phase, progesterone levels gradually increase and the cervical mucous becomes thicker and highly viscous, acting as a barrier to advancement of spermatozoa.[71] Hence, pathogens may be more likely to ascend to the upper genital tract when oestrogen levels are high in the follicular phase than in the luteal phase when progesterone is the dominant hormone. Some evidence to support this comes from a study of 104 women with salpingitis; in which women with an associated gonorrhoea or chlamydia infection were more likely to have PID symptoms commence within the first seven days of the menstrual cycle compared to women with non-chlamydial, non-gonococcal salpingitis.[72]

The use of oral contraceptives has been thought to offer some protection against ascending infection. Studies from the 1980s and 1990s have reported lower rates of symptomatic chlamydial PID for women using oral contraceptives compared for women with a chlamydia infection and not using oral contraceptives.[73 74] Another explanation for this finding was that oral contraception may decrease the severity of the symptoms of upper genital tract inflammation, thereby being associated with a greater risk of sub-clinical PID.[75] For women with gonorrhoea infection, this protective association between oral contraception and PID has not been observed.[73] More recent studies have shown no difference for oral contraception users[76] or a greater risk of endometrial chlamydia infection for oral contraception users in multivariable models adjusting for other STIs and sexual activity.[77] Such conflicting evidence has been postulated to occur because earlier studies showing reduced PID risk with oral contraception use were based on higher hormonal doses than more recent studies.[3] Some explanation for increased ascension in oral contraception users comes from invitro and animal studies, showing increased chlamydial attachment to human endometrial cells with oestrogen,[78] and increased chlamydia ascension and upper genital tract pathology with oestrogen and progesterone treatment.[79]

Endocervical epithelium and cervical ectopy

Cervical ectopy occurs when the columnar epithelium of the cervical canal extends beyond the endocervix into the vagina. The presence of cervical ectopy is related to oestrogen levels and is more common in adolescent women, pregnant women and women taking hormonal contraception.[61] Cervical ectopy results in a larger area of columnar epithelium that is thinner than the normal squamous epithelium of the vagina and has been hypothesised to increase susceptibility to STIs thereby contributing to higher PID rates.[28 75] Higher chlamydia rates have been reported in women with cervical ectopy than for women without ectopy. A study of over 200 young female UK genito-urinary medicine clinic attendees reported a chlamydia diagnosis in 37.4% of women with ectopy compared to 21.8% without,[80] and, in 700 young sexually active South African women a chlamydia diagnosis was more likely (AOR 1.78, p=0.033) for women with cervical ectopy than without.[81] Furthermore, young South African women (aged under 19 years) with cervical ectopy were more likely to have a HIV infection.[81]

Other factors

PID can also follow procedures that interrupt the cervical barrier such as for IUD insertion, surgical termination of pregnancy or hysteroscopy (see also Section 2.3).[4 82-85] Concern about the safety of IUDs, particularly during the 1960s[86] and 1970s (being a period when PID rates were high), led to a large number of case control studies that investigated and reported associations between the IUD and PID. However, the same magnitude of risk in prospective studies was not observed. Debate about the biases in case control studies (such as over-diagnosis of PID in women with an IUD insitu) led to systematic reviews on the relationship between PID and IUDs.[27 87] While uterine instrumentation can increase the risk of PID, this risk is higher for women with an STI and limited to around three weeks post procedure.[27 82 88]

Other possible factors in PID aetiology include spermatozoa and smoking. Spermatozoa with attached chlamydia have been detected in the peritoneal fluid of women with salpingitis suggesting they have acted as a vector to the upper genital tract.[89] Associations between cigarette smoking and PID have been reported. A case control study in the USA, reported a relative risk of 1.7 (95%CI: 1.1, 2.5) of hospitalisation for PID among current smokers compared to controls with a non-gynaecologic condition, however , a dose response relationship was not observed[90] and this finding has not been consistently reported.[19 87 91] While it has been postulated that smoking may affect the immune response or oestrogen activity, thereby increasing risk of PID, it is possible that other factors such as being in a lower socio-economic group where rates of smoking, STIs and health seeking behaviour are different could influence this finding.[4 28]

2.1.3 Clinical manifestations

The key feature of mild to moderate PID is recent onset (less than 30 days duration) of bilateral lower abdominal or pelvic pain. Other features may include mucopurulent cervical discharge, intermenstrual bleeding, dyspareunia, or, presence of any one of cervical motion tenderness, adnexal tenderness or uterine tenderness detected on bimanual examination.[2 6 12 13] Most mild to moderate PID cases can be managed in ambulatory care settings,[13] and is estimated to represent around a third of PID cases.[6] Different pathogens can be associated with different clinical features. Women with chlamydial PID may experience mild or no symptoms, however tubal damage appears to be more severe and is thought to occur as part

of the immune response to the infection (see also Section 2.2.1).[6 92] In contrast, gonorrhoeal PID often involves an acute onset of abdominal pain and a direct infection of the epithelial lining of the fallopian tube leading to tubal damage.[6 12]

Around 5-10% of women with overt PID symptoms will have severe PID.[6] The clinical presentation of severe PID can include systemic features such as fever, nausea, vomiting, and signs of peritonitis such as abdominal guarding. Severe PID is often associated with gonorrhoea infection and managed on an in-patient basis. Other features may include an elevated white blood cell count, erythrocyte sedimentation rate and C-reactive protein. Some women will also develop right-upper-quadrant pain associated with peri-hepatitis (also termed Fitzhugh-Curtis syndrome) and tubo-ovarian abscess can occur.[6 12] Fitzhugh-Curtis syndrome was identified in 4% of young US women with mild to moderately severe PID that involved chlamydia as the most common PID pathogen.[93]

Many women experience no signs or symptoms as infection ascends to the upper genital tract to cause sub-clinical (or silent) PID or silent salpingitis.[2 6] Despite the absence of symptoms, tubal damage can occur and past chlamydial infection (based on serum chlamydia antibodies) has been reported in up to 79% of women undergoing infertility investigations,[92 94] with 69% of women with tubal infertility having no history of PID.[92] As noted earlier (Section 2.1.2), similar findings of tubal damage as observed on biopsy and evidence of past chlamydia infection have been found for infertile women with a history of PID and for infertile women without a history of PID.[54] However, while a Swedish study also found that 69% of women with tubal factor infertility reported no history of PID, another finding was that only 11% of women with tubal pathology reported never having had abdominal or pelvic pain.[95] The findings from this study suggest that many PID cases that cause reproductive damage are undiagnosed rather than being completely asymptomatic.

2.2 PID pathogens

Knowledge of the pathogens involved in PID is critical so that anti-microbial therapy can target the likely pathogen, for clinicians to know the risks of PID associated with a pathogen, and to inform public health responses to PID and STIs. There are still evidence gaps regarding PID pathogens.[96] The STIs, chlamydia, gonorrhoea,[7] *M. genitalium* [8 9] are known PID causes and a range of bacteria, many endogenous to the vaginal microbiota or occurring in increased

concentrations with bacterial vaginosis have been isolated from the upper genital tract of women with PID.[10 50 97] Enteric, respiratory, and novel bacteria have also been identified.[1 2 49 50 97-99] The role of many of these microbes in PID aetiology is unknown.

The proportion of PID cases caused by different pathogens will vary between country, health setting and risk group, depending on the underlying prevalence in the population. The method of PID diagnosis (e.g. clinical versus laparoscopic) and study sample size will also influence the proportions of pathogens identified. In US and European based studies during the 1970s to 1990s, chlamydia was detected in 14-65% of laparoscopically diagnosed PID cases.[4] In the US, baseline findings from the Pelvic Inflammatory Disease Evaluation and Clinical Health (PEACH) study reported that 40% of women with clinically diagnosed PID had a chlamydia and /or gonorrhoea infection[100] with *M. genitalium* detected in 15% of a subset.[101] Another US study during the 2000s identified chlamydia in 10%, gonorrhoea in 4.4% and chlamydia and gonorrhoea coinfection in 2.6% of women with clinically diagnosed PID.[18] Up to two-thirds of PID cases may have no infection identified.[19] For Australia, there are limited reports about PID pathogens. A case control study among sexual health clinic attendees between 2002 and 2006 identified chlamydia in 19.5% of women with a PID diagnosis.[44]

This Section will cover the sexually transmitted pathogens, *Chlamydia trachomatis, Neisseria gonorrhoeae* and *M. genitalium.* It will also cover bacterial vaginosis due to the strong association with PID and the importance of the vaginal microbiota with bacterial vaginosis and PID aetiology. Although endemic in some Aboriginal and Torres Strait Islander populations,[21] *T. vaginalis* will not be covered, due to infrequent reported associations for upper genital tract infection,[11] due to this infection not being notifiable in most Australian states and Territories(21) and to its infrequent diagnosis in women in general in Australia.[102] Detail of recent patterns in chlamydia and gonorrhoea diagnoses for Australia is provided in Section 2.5.2.

2.2.1 Chlamydia and PID

Chlamydia trachomatis is a gram-negative bacterium that can be classified into 15 serovars, distinguishable by differences in the major outer membrane protein. The incubation period

is typically around 5 to 10 days.[103 104] Serovars A to C are associated with trachoma and serovars L1, L2, L3 cause lymphogranuloma venereum. Serovars D to K cause urogenital infections by infecting the columnar epithelium of the lower genital tract from where they can ascend to the upper genital tract to cause PID in women or epididymitis in men, and, can also infect respiratory and ocular tissues.[103 104] Chlamydia can also be transmitted vertically from mother to newborn during a vaginal delivery. [103 104] Serovars D, E, F account for up to 67% of genital infections in women and 75% of genital infections in men and can be transmitted by oral, vaginal or anal sex.[103-105]

Diagnosis of chlamydia infection is generally based on nucleic acid amplification tests (NAATs). For women these are conducted on cervical or vaginal swabs or urine specimens and are highly sensitive to *C. trachomatis.*[13] Prior to NAATs, chlamydia diagnosis was based on culture or enzyme immunoassays, for which diagnostic sensitivity is lower.[106 107]

Most chlamydia infections are asymptomatic, with some reports of up to 85-90% for women and men[108] and other reports suggesting that around three-quarters of incident infections for women[109] and around one-half of incident infections for men are asymptomatic.[110] However clinical examination has shown that around a third of women with asymptomatic infection have local signs of infection, the most common being mucopurulent cervical discharge or hypertrophic cervical ectopy.[108] Symptoms of female lower genital tract infection can include changes in vaginal discharge, dysuria, postcoital or intermenstrual bleeding.[105] Women with chlamydial PID are often asymptomatic or have a clinically milder disease than gonorrhoeal PID. However tubal damage can be more severe than for gonorrhoeal infection and occurs secondary to the immune response to infection.[1 105 111]

The natural course of chlamydia infection in humans is varied. Without treatment, some infections will resolve spontaneously, others will persist over long periods without complication and others will progress to complications[112-114] Figure **2** shows the relationship between chlamydia infection and possible progression to sequalae for woman.[115] Quantifying the natural history of chlamydia is difficult. It is not possible to know the timepoint when an infection was acquired, diagnosed infections are generally treated, and, in studies that have followed untreated infections it is often uncertain whether repeat positive tests represent infection persistence or reinfection after clearance of an infection.[113] Other methodological

issues have included small numbers of participants or non-generalisable findings from studies undertaken in high prevalence populations. Available evidence has shown that clearance of untreated chlamydia infections increases over time, with around one half of infections spontaneously clearing within a year, and, a small amount of infections persisting for up to four years.[112-114] A recent synthesis of evidence explained the heterogeneity in studies of chlamydia duration by distinguishing between prevalent (detected via screening) and incident (detected in clinics) infections, and, reported the mean duration of chlamydial infection in women (including symptomatic and asymptomatic infections) to be 1.03 years.[109] Different chlamydia serovars have been found to be associated with different serological responses in urogenital infection for women and men,[116] and to have different associations with symptoms for women.[117] Chlamydia clearance rates have been shown to vary by serovar, and, to be slower for younger woman,[112] although older women may have had past exposure to chlamydia.

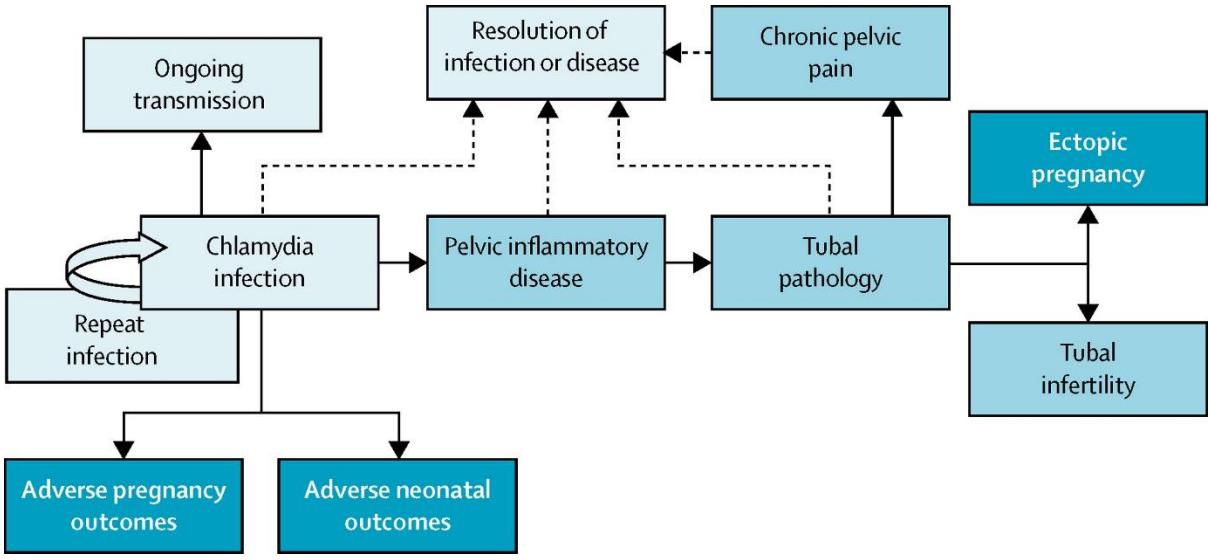

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Figure 2 Natural history and sequelae of *Chlamydia trachomatis* infection in women

Risk of pelvic inflammatory disease associated with chlamydia infection

The reasons that some chlamydia infections ascend to the upper genital tract and others do not are not fully understood, but appear to be due to a combination of factors.[111] Pathogen load appears to be associated with the propensity for chlamydia infections to ascend, with high chlamydial antibody titres in some studies associated with chlamydial PID[49] or severe

tubal damage.[118] Analyses of data from the PEACH study showed that higher chlamydial antibody titres were associated with higher recurrent PID and reduced pregnancy rates for women with mild to moderate PID.[119]

Repeated chlamydial infection is important. Higher rates of PID and other reproductive sequelae have been shown with repeat chlamydial infections. A retrospective cohort among 11,000 women in the US, found a PID diagnosis was more likely for women who had two or more chlamydia diagnoses and that higher ectopic pregnancy rates were associated with more than one chlamydia diagnosis. Although, in this study, it is possible that clinicians were more likely to diagnose PID for woman with repeated chlamydia infection.[120] The PEACH study, found higher rates of self-reported PID recurrence, chronic pelvic pain and infertility were associated with less condom use,[121] suggesting repeated exposure to chlamydia infection. A population-based cohort in Denmark (1995 to 2012) found that compared to a negative chlamydia test, the risk of a PID diagnosis in hospital (inpatient, outpatient or emergency department) was 50% higher for women with one or more positive test and 67% lower in women who had never been tested. A repeat chlamydia diagnosis was associated with a 20% higher risk of PID.[122] It is not clear if the PID risk is increased because of a longer cumulative time of being infected or whether the risk increases with each additional infection.[22]

Although chlamydia infection is known to cause PID, infertility and ectopic pregnancy, difficulties in conducting natural history studies mean that estimates of the incidence for these sequalae are limited. Several prospective observational[123-128] and controlled trials[39 129-131] have examined the risk of PID after untreated chlamydia infection. A retrospective cohort also assessed the risk of PID after chlamydia testing in a hospital emergency department or obstetrics or gynaecology out-patient clinic.[132] These studies have varied in design, setting, population, size and length of follow up, making interpretation and comparisons difficult.

A summary of the proportion of PID cases diagnosed in untreated chlamydia cases from prospective studies is provided in Table 1. For high risk populations, PID has been diagnosed in the two weeks between testing and treatment for 2–5% of chlamydia infections in STI clinics[22 124 127] or hospital ambulatory settings[132] and up to 13% of chlamydia infections in a correctional facility.[128] Over 1-3 months, PID rates of 20-30% among women with untreated

chlamydia infection have been reported[126 133] although generalisability of these findings is limited by the small sample size for these studies and by gonorrhoeal coinfection in one study. Over 12 months, no PID cases were reported for asymptomatic women with chlamydia detected during pre-employment screening,[114] however PID was defined by self-report and study numbers were small. The Prevention of Pelvic Infection (POPI) randomised controlled trial found that over 10% of untreated chlamydia infections among young female students developed into symptomatic PID over 1 year.[39] Two reviews[22 134] focussing on the risk of PID after untreated chlamydia infection summarised the key findings and assessed the validity for many of the studies listed in Table 1. Due to variable rates and validity these reviews could not determine an overall estimate and identified the need for further prospective studies on the natural history of chlamydia infection and assessing rates of symptomatic PID and other reproductive sequelae. Although mathematical modelling has estimated that 22% of chlamydia infections will progress to PID.[135]

Table 1 Prospective studies assessing PID risk after untreated chlamydia infection

Study (year)	Study type	Setting and population	Follow up	Women with untreated chlamydia N	PID n (%)
Rees (1980) [125]	Observational	STI clinic High risk female attendees	3 months	67	5 (7.5)
Paavonen (1980) [126]	Observational	STI clinic Asymptomatic female partners of men with non-gonoccocal urethritis	1 month	15	3 (20.0)
Stamm (1984) [133]	Observational	STI Clinic Chlamydia positive women (coinfected with gonorrhoea)	7 weeks	20	6 (30.0)
Rahm (1986)[123]	Observational	Screening (contraception clinic) Asymptomatic adolescents	3 months	109	4 (3.9)
Hook (1994)[127]	Observational	STI clinic High risk asymptomatic young women	2 weeks	93	3 (3.2)
Morre (2002) [114]	Observational	Screening (pre-employment) Low risk asymptomatic women	I year	30	0
Geisler (2008)[124]	Observational	STI clinic Asymptomatic young women	2 weeks	115	2 (2)
Risser (2012)[128]	Observational	Screening (corrections facility clinic) Chlamydia or gonorrhoea positive young women	2 weeks	74	10 (13.5)
Oakeshott (2010) [39]	RCT	Screening (students) Low risk asymptomatic young women	1 year	74	7 (9.5)

Recent evidence for the risk of PID following chlamydia infection is provided in a comprehensive synthesis and analysis of data from prospective controlled studies[109]

comprising the POPI study,[39] two RCTs of chlamydia screening,[130 131] and a prospective cohort within an STI clinic.[125] Using a Bayesian approach, Markov models were developed that estimated the PID rate in chlamydia infected women and the probability that incident chlamydia will cause PID. These models accounted for the time-period of follow up, differences in progression rates to PID for chlamydia positive and chlamydia negative women, clearance of chlamydia infection, that chlamydia cases detected through screening have had a period of time without developing PID, and for reinfection rates after chlamydia treatment. A key finding was that for new chlamydia infections in women, 14.8% will progress to symptomatic PID and 17.1% to PID if asymptomatic PID is included.[109] A further synthesis and modelling of prospective, retrospective and routine data sources estimated that 19.7% of PID for women aged 16 to 44 years was attributable to incident chlamydia infection.[109] These modelled estimates adjusted for under-ascertainment of chlamydia in PID cases in the retrospective studies, thereby increasing the PAF from 14.5%.[109]

2.2.2 Gonorrhoea and PID

Neisseria gonorrhoeae is a gram-negative bacterium that causes the STI gonorrhoea. For women, *N gonorrhoeae* can infect the mucous membranes of the lower genital tract including the cervix and urethra, and the pharynx, rectum and conjunctiva can also be infected. The incubation period between infection acquisition and development of symptoms for female gonoccocal infections has been reported at a median of 9-10 days in a sample of 96 women attending a Swedish venereal disease clinic[136] and around 13 days in a small sample of US women.[137] Symptoms may include dysuria, increased vaginal discharge or inter-menstrual bleeding, although 85% or more of female infections maybe asymptomatic or symptoms may not be recognized until complications such as PID have developed.[13 136-138]

Like chlamydia, testing for gonorrhoea in many high-income countries and settings is now predominantly conducted using NAATs. For women, NAATs are conducted on endocervical or vaginal swabs or urine specimens and can be simultaneously tested for gonorrhoea and chlamydia.[13 137] Although NAATS are more sensitive than culture based techniques, the collection of specimens for culture and antimicrobial susceptibility testing is critical to inform individual patient treatment and to contribute to surveillance systems established to monitor trends in antimicrobial sensitivities of gonorrhoea infection.[13 21 139]

The clinical picture of gonorrhoeal PID is often severe, involving acute onset of pelvic pain or markers of inflammation (e.g. raised white blood cell count, erythrocyte sedimentation rate or C reactive protein) compared with chlamydial or *M. genitalium* PID.[1 12 140] Gonorrhoeal infection appears to directly damage the epithelial lining of the fallopian tubes to cause the abrupt onset of symptoms, thereby prompting women to seek healthcare earlier than for chlamydial PID.[7]

Although the relationship between gonorrhoea, PID and infertility has long been recognised[7 51 141] much of the evidence for the natural history of gonorrhoea in women stems from studies during the gonorrhoea epidemics of the 1960s to 1980s that suggested up to a fifth of gonorrhoeal infections in women may progress to PID.[4 7 52 55 137 142] More recently, PID has been diagnosed in 13% of chlamydia or gonorrhoea-infected adolescents in the 7–15 days between testing and treatment.[128] A number of modelling studies have investigated the cost effectiveness of gonorrhoea and chlamydia control. In the absence of empirical evidence for the progression of gonorrhoea to upper genital tract infection, many have assumed the same characteristics or probabilities for gonorrhoea as for chlamydia infection.[135 143 144]

2.2.3 Mycoplasma genitalium and PID

First cultured in 1981 from two men with non-gonococcal urethritis (NGU), *Mycoplasma genitalium* is the smallest known free-living organism that is capable of self-replication.[145 146] There are 16 mycoplasmal species found in humans, with *M. genitalium* being one of four mycoplasmas known to have pathogenic properties. Because *M. genitalium* is difficult to culture and it cannot be visualised on Gram stain (due to lack of a cell wall), research into its pathogenic properties only proliferated after development of polymerase chain reaction (PCR) technology and NAATs in the 1990s. Since then, *M. genitalium* has been consistently associated with NGU, detected in up to 25% of symptomatic men with NGU,[146] and, studies showing high concordance and the same sequence type between sexual partners provided evidence for its sexual transmission.[147 148]

For women, *M. genitalium* has received attention for its associations with cervicitis,[149 150] endometritis,[151], PID,[152 153] infertility and pre-term delivery,[146] although evidence for the relationship with upper genital tract infection has been inconsistent.[154-156] A prevalence study

during the 1990s, reported that *M. genitalium* was detected by PCR in 39% of vaginal and 21% of cervical specimens among female sexual clinic attendees presenting with abnormal discharge, although no association with cervicitis was shown on multivariable analysis.[155] A study based in a US sexual health clinic detected *M. genitalium* in up to 28% of women with cervicitis[157].[146] In the 2000s, *M. genitalium* was identified by PCR in 2.1% of women attending a Swedish gynaecological outpatient service, and PID was diagnosed in 4.9% of *M. genitalium* cases (excluding *M. genitalium* and chlamydia coinfections). Multivariable analysis showed cervicitis and PID were independently associated with *M. genitalium*.[158] A recent meta-analysis[159] has shown *M. genitalium* to be highly prevalent in some population groups including a pooled estimate of 15.9 (95%CI 13.5, 18.9) for community based female sex workers. Several reviews,[146 160] and, a meta-analysis of the association of *M. genitalium* with female genital tract disease have been conducted,[9] providing evidence for *M. genitalium* as a PID pathogen. Expressed as odds ratios, the risk of PID associated with *M. genitalium* ranged from 0.2 in a 1987 study using serological samples[161] to 12.3 in a 2003 study using PCR,[162] with a pooled odds ratio of 2.1 (95%CI 1.3, 3.5).[9] After exclusion of serological based studies, the pooled odds ratio was 2.7 (95%CI 1.6, 4.7). The meta-analysis also reported an association for cervicitis (OR 1.7, 95%CI 1.4, 2.0) and infertility (OR 2.4, 95%CI 0.9, 6.3).[9]

NAAT diagnostics are now available to test for *M. genitalium* from many anatomical sites including vaginal and endocervical swabs and urine specimens, however their use has been largely limited to research or specialised clinical settings where symptomatic patients are likely to present.[163] In light of evidence for adverse female reproductive impacts, high prevalence among high risk populations, and concern about growing antibiotic resistance, recent debate has focused on increasing availability of testing for *M. genitalium,*[163 164] however *M. genitalium* prevalence in asymptomatic populations is less well known. In Australian primary care clinics, *M. genitalium* was detected in 2.4% of young female attendees.[152] The meta-analysis[159] referred to above has contributed to knowledge of the extent of *M. genitalium* in asymptomatic populations, reporting a prevalence of <1% for pregnant women and asymptomatic clinic patients, and for the general population a prevalence of 1.3% in high income countries. *M. genitalium* prevalence was higher (3.9%) but more variable (ranging from 0.8 to 9.1%) in general populations in low to middle income countries. Based on these findings, *M. genitalium* testing for asymptomatic clinic attenders

was considered unjustified.[159] However, targeted *M. genitalium* testing of symptomatic high risk women, including with suspected PID, is recommended in many clinical settings.[110 165]

2.2.4 Bacterial vaginosis and PID

Bacterial vaginosis is a clinical syndrome associated with changes in composition of the vaginal flora, generally from a lactobacillus dominated environment to one with a proliferation of *Gardnerella vaginalis, Mycoplasma hominis* or anaerobic bacteria. Women with bacterial vaginosis may present with general symptoms of vaginal inflammation including pain, itching, a burning sensation or an offensive vaginal discharge.[63 166 167]

The reasons for this shift in vaginal flora are not fully known, although sexual transmission is suggested by the epidemiological associations for this condition. Bacterial vaginosis occurs more often among women who report a change of sexual partner, high numbers of lifetime sexual partners, young age at sexual debut and there is strong conformity between female sexual partners.[167-169] Other associations for bacterial vaginosis include douching for hygiene[170] which is thought to promote loss of lactobacilli, and also smoking, recent antibiotic use, and low socio-economic status, although these could be surrogates for other risk factors.[63] Changes in the vaginal microbiome through the menstrual cycle may also mean that women have intervals of increased susceptibility to infection.[67] There is some evidence to suggest that current use of hormonal contraception, the luteal phase of the menstrual cycle, and condom use are protective for bacterial vaginosis.[63 167 169]

Bacterial vaginosis is extremely common, with prevalence estimates ranging from 12% for Australian women,[171] to 29% among North American women,[172 173] and over 50% for women in sub-Saharan Africa.[174] Prevalence is widely variable between different ethnic groups, ranging from 23% to 52% between white non-Hispanic and black non-Hispanic women in the US,[173] most likely associated with different vaginal CSTs in different ethnic groups.[65]

Women with bacterial vaginosis are at increased risk for PID and other reproductive tract pathology including STI acquisition, cervicitis, spontaneous abortion, pre-term delivery, post-operative infections and post-partum endometritis.[169 173] However a direct causal role for PID has not been established. An important issue with epidemiological and aetiological studies of bacterial vaginosis is that there are different definitions of this condition. In clinical settings

bacterial vaginosis diagnosis is often based on Amsels criteria that are met if three of the following four criteria are present; i) a homogenous thin white vaginal discharge, ii) high vaginal pH (> 4.5), iii) a fishy vaginal odour, and iv) presence of clue cells on gram stain and microscopy of vaginal smears.[57 63 110 175] Alternatively, bacterial vaginosis is diagnosed by Nugent scoring in which vaginal smears are gram stained then assigned a score of 0-10 based on relative proportions of large gram-positive rods (lactobacilli) and gram negative rods (such as *Gardnerella*) or gram variable rods. A score of 0 to 3 is taken to indicate normal vaginal flora, 4 to 6 to indicate a disturbance of flora, and 7–10 as bacterial vaginosis.[57 166 167 175 176] Bacterial vaginosis is often diagnosed in association with PID or acute endometritis[166 177-179] and is associated with incident chlamydial and gonorrhoeal infections.[167 180] In other studies no association between bacterial vaginosis and incident PID has been found,[50] although high levels of gram negative anaerobes have been present before or at the time of PID diagnosis, independently of gonorrhoea or chlamydial infection.[50 97 166 177] Based on these findings, anaerobic cover for PID treatment is recommended.

2.3 PID Risk factors

Knowledge of factors contributing to a woman's risk for PID is important for supporting timely diagnosis and management, and, to inform prevention and control measures.[28] The risk of PID is higher for women with a current STI (chlamydia, gonorrhoea, *M. genitalium)*, a history of an STI, or repeated infection.[19 26 49] PID occurs almost only in women who are sexually active and the main risks are largely those for STI acquisition. Socioeconomic and racial disparities in PID rates have been reported and most likely reflect higher STI prevalence among lower socio-economic or specific racial groups.[7 19 85 181] Availability or limited access to health care for timely STI diagnosis and management could also contribute to PID risk.[28] High PID rates have been reported among young women,[128] sex workers,[26] non-white North American women[85]and Aboriginal and/or Torres Strait Islander women in remote Australia[182] for whom high rates of infertility have also been reported.[183]

A large body of evidence shows that younger women experience higher PID rates than older women[184-187] and that age is an independent predictor for PID.[19 188 189] This association is interrelated with a wide range of demographic, behavioural, physiological, and pathogenic factors, some of which have a direct causal relationship and others having an indirect

relationship with PID development.[28] Younger women are at higher risk of PID and STI acquisition than older women due to several physiological characteristics. As noted in Section 2.1.2, these include lower concentrations of protective chlamydial antibodies, larger cervical ectopy zones,[61 80 81] and more penetrable cervical mucous.[7] Behavioural risk factors for PID include young age at sexual debut, multiple sexual partners, recent partner change, and inconsistent use of barrier contraception methods,[19 85 189-191] although in terms of the PID causal pathway these are also risk factors for STI acquisition.[28] Consistent condom use among women with PID has also been shown to reduce the risk of recurrent PID, chronic pelvic pain and infertility.[121] The risk of a PID diagnosis is further increased for women who have multiple or recurrent chlamydia or gonorrhoea infections diagnosed.[40 120 192]

Other risks for PID include uterine instrumentation such as for IUD insertion, dilatation and curettage, or surgical termination of pregnancy that can facilitate ascent of micro-organisms from the vagina or cervix into the endometrial cavity.[4 19 82-85] As noted in section 2.1.2, the IUD has been debated for its association with PID, with these associations potentially a barrier to more widespread uptake of the IUD. Much of this debate occurred during the 1960's and 1970s[86] when PID rates were high. Concern about IUDs was also fuelled by a meta-analysis of studies published between 1974 and 1990 that reported positive associations between IUD use and PID.[193] However, many studies at this time used a case control design that could be biased by over-diagnosis of PID in women with an IUD insitu. Other meta-analyses have stratified studies by design type. Showing that IUDs do not have the same risk of PID in prospective studies as retrospective studies, and, that the risk of PID at the time of IUD insertion is higher for women with an STI compared to women without an STI, and, that the absolute risk is low irrespective of having an STI and is limited to the three weeks post procedure.[27 82 87 88]

A role for vaginal douching in PID risk has also been debated, based on many women with PID reporting a history of douching.[85 194-196] Although recent evidence from prospective studies found no difference in the risk of PID for women who do or don't report douching[197] and suggested a different temporal relationship – that an offensive vaginal discharge with PID may lead to increased douching. One explanation for the association between smoking and PID been that smoking may affect the immune response or oestrogen activity.[4 28] Smoking is also

associated with an increased risk of ectopic pregnancy and infertility. However, the association for smoking could reflect different STI risk and health seeking behaviours in different socioeconomic groups. Of course, any risk of PID after uterine instrumentation or other factors will also be influenced by the underlying prevalence of STIs in different geographic regions and population.[84 198]

2.4 Diagnosis and management of PID

2.4.1 PID diagnosis

Most PID diagnoses are clinically made, but due to the wide range of possible signs and symptoms, it is difficult to diagnose. There is no non-invasive sensitive and specific test for PID, and, women with PID can be asymptomatic or have non-specific symptoms.[13] Clinical diagnosis of PID relies on information gained from the physical examination, the medical history and investigations conducted.

Recent-onset bilateral low abdominal pain is a key feature but can have many causes and it is important that differential diagnoses are excluded. Some alternative causes of low abdominal pain include ectopic pregnancy, appendicitis, urinary tract infection, pyelonephritis, and, ovarian pathology such as rupture or torsion.[12 13 199] Chronic conditions such as endometriosis, dysmenorrhoea or irritable bowel syndrome should also be considered. Prompt diagnosis, treatment and clinical review of PID is essential to reduce the risk of progression to long-term sequelae, and once emergency differential conditions are excluded, PID treatment should be commenced. The minimum diagnostic criteria being any one of uterine, cervical motion or adnexal tenderness on bimanual examination in sexually active women with recent onset pelvic pain where no other cause is identified.[13 32 200] The rationale being that over-diagnosis is better than under-diagnosis as the risks of antibiotics are potentially less than from possible sequelae associated with ongoing untreated infection.[2 13]

Laparoscopy has in the past been considered the gold standard for PID diagnosis. It enables direct visualisation of the fallopian tubes for diagnosis of salpingitis and supports identification of upper genital tract pathogens. However, laparoscopy has high inter-observer variability, and, it may not detect endometritis or early inflammation of the fallopian tubes.

Furthermore, laparoscopy is invasive and impractical for most clinical settings where mild to moderate PID is diagnosed.[6 12 13 199]

Gaining an accurate history is essential to support or exclude a PID diagnosis.[13 199] The history should gain a description of the pain. PID pain is usually recent onset (days to weeks) bilateral mild to moderate pain in the lower abdomen that may resemble menstrual pain. Whereas, ectopic pregnancy or appendicitis associated pain is often more acute and unilateral or radiates to the right iliac fossa. Around 5% of PID cases may exhibit right-upper-quadrant pain, which could be misdiagnosed as cholecystitis, but indicates peri-hepatic inflammation or Fitz-Hugh-Curtis syndrome and women with severe PID may have systemic features including fever, nausea and vomiting. Further questioning of women with suspected PID could ascertain if they have experienced dyspareunia, postcoital or intermenstrual bleeding or altered vaginal discharge (may suggest cervicitis and PID), and, when symptoms started (PID pain often starts after menstruation). The history should also cover contraception, sexual and menstrual information to ascertain if a pregnancy is likely, whether a woman is at increased risk of an STI such as following a recent change of sex partner, or other information such as a recent IUD insertion or procedure involving uterine instrumentation.[199]

The clinical assessment should include abdominal palpation and pelvic examination. Bimanual pelvic examination is conducted to exclude uterine or adnexal abnormalities, and, to assess for adnexal or cervical motion tenderness (also termed cervical excitation) that often occur with movement of the cervix when pelvic inflammation is present. If on bimanual examination, cervical motion, uterine or adnexal tenderness are not present, the diagnosis of PID should be reappraised. Speculum examination should be conducted to visualise the cervix and identify any cervical bleeding, friability, mucopurulent discharge or erythema that indicate cervicitis and further support a PID diagnosis.[13 110 199]

Investigations for all women with suspected PID should include a pregnancy test to help exclude an ectopic pregnancy.[13 110 199] High vaginal and/or endocervical swabs, and, also first pass urine specimens should be tested for chlamydia and gonorrhoea using NAAT, and, also of endocervical swabs for *M. genitalium* in settings where these tests are available. Microscopy, culture and antibiotic sensitivity testing should also be conducted for women with a positive gonorrhoea test or cervical mucopurulent discharge. Assessment of high

vaginal swabs can help to diagnose other infections, such as bacterial vaginosis. Most women with PID have mucopurulent cervical discharge or presence of leukocytes on microscopic evaluation high vaginal swabs. If these are not present a PID diagnosis is unlikely.

Diagnostic certainty (i.e. specificity) increases with each clinical feature that is present in addition to one of the minimum criteria (i.e. uterine tenderness, cervical motion tenderness, adnexal tenderness). Additional criteria to enhance a PID diagnosis include one or more of: elevated temperature, cervical friability or mucopurulent discharge, elevated erythrocyte sedimentation rate or C-reactive protein, abundant vaginal leukocytes, and a lower genital tract chlamydia or gonorrhoea infection. However, requiring all features to be present comes at the expense of diagnostic sensitivity and would reduce the number of cases that are identified.[13 16 201 202 203] A rapid improvement in symptoms after commencement of antibiotic treatment further supports a diagnosis of PID.

Other investigations can include transvaginal ultrasound or magnetic resonance imaging (MRI) to identify tubo-ovarian abscess or thickened fluid filled tubes, endometrial biopsy to histologically confirm endometritis, or, Doppler ultrasound[204] to detect altered blood flow (or hyperaemia) with tubal inflammation. However, these investigations are variable in their sensitivity and specificity[202] and are not part of routine practice. MRI is expensive and not always available, interpretation of trans-vaginal ultrasound is variable between operators, and, endometrial biopsy is invasive and timeframes for reporting of results can delay diagnosis.[2 12 13 16]

In view of the uncertainties around clinical diagnosis of PID and the risks of sequelae from delayed diagnosis and treatment, development of a non-invasive biomarker to identify women with upper genital tract inflammation is a research priority.[205] Elevated serum levels of inflammatory proteins and cytokines have been reported in patients with clinically diagnosed PID[206 207] and different ribonucleic acid biosignatures (many involved in inflammation) have been identified in peripheral blood of a small sample of PID cases[208] and also in mice,[209] however objective tests for clinical are not available.

2.4.2 PID management

In view of the diagnostic challenges and potential consequences of untreated PID, clinical guidelines recommend a high suspicion for PID diagnosis and that PID treatment is initiated promptly. [13 32 200] PID antibiotic regimens should provide broad spectrum cover for the likely pathogens, noting that the importance of different pathogens will vary between geographic regions and population groups. Recommendations for PID treatment advise a regime to cover chlamydia infection, and to consider gonorrhoeal infection and anaerobic bacteria (e.g. with bacterial vaginosis), and more recently to cover *M. genitalium* if diagnosed.[13 32 200] Although several PID antibiotic regimens have been shown to be effective in achieving clinical and microbiologic cure, there is limited evidence regarding the optimal regime for avoiding long term complications, or the superiority of one regime versus another.[13 210-214]

Antibiotic treatment should be commenced immediately that a provisional diagnosis of PID is made, without waiting for test results. Whether a woman with PID is managed in hospital or as an outpatient will depend on her clinical presentation and the clinician's judgement. Hospital admission should be considered for women when a surgical emergency cannot be excluded, for severe illness, tubo-ovarian abscess or pregnancy, poor or no response to outpatient treatment, or intolerance to oral therapy.[12 13 199 200]

For mild to moderate PID, treatment is generally an outpatient regime of oral antibiotics over 14 days with use of ceftriaxone to cover suspected or confirmed gonorrhoea.[30-32] Australian guidelines for PID management in primary care recommend oral doxycycline and metronidazole, with single dose intramuscular or intravenous ceftriaxone. Antibiotic sensitivity testing can be conducted for gonorrhoea, and, in view of high levels of *M. genitalium* resistance to azithromycin, [215 216] Australian guidelines recommend Moxifloxacin for 14 days if *M. genitalium* is diagnosed for a woman with PID (Table 2).[200] However, *M. genitalium* testing in Australia is only routinely available in specialist settings such as sexual health clinics.[21] For patients who may not adhere to a daily medication regime, azithromycin as a single dose immediately and one week later is recommended in lieu of doxycycline.[200] Metronidazole is often the choice for anaerobic cover, but can be poorly tolerated.[12] Other anaerobic agents (e.g. amoxicillin-clavulanate) may achieve an equivalent microbial cure.[214] Inpatient management, when required consists of intravenous therapy (Table 2) until

symptoms and signs improve and then followed by oral therapy to complete 14 days of antibiotic treatment. For women with an IUD; removal (along with contraceptive advice) should be considered if they have not improved within 2-3 days.

Table 2 Antibiotic therapy for PID

PID type	Recommended antibiotic treatment*
Mild to moderate Outpatient treatment	Ceftriaxone 500mg in 2mL of 1% lignocaine by intra-muscular injection, or 500 mg intravenously PLUS Oral metronidazole 400mg twice daily for 14 days PLUS Oral doxycycline 100mg twice daily for 14 days
Severe Inpatient treatment	Ceftriaxone 2g intravenously, daily OR Cefotaxime 2g intravenously, three times daily PLUS Azithromycin 500mg intravenously, daily PLUS Metronidazole 500mg intravenously, twice daily

* If *M. genitalium* is confirmed also treat with Moxifloxacin 400mg daily for 14 days

All women with PID should be given advice about rest and appropriate analgesia if needed, and, to avoid unprotected sexual intercourse until both the woman and sexual partner/s have completed treatment and follow up. Advice and education (including written information) should also be provided about how PID was acquired, the potential long-term consequences and how repeated infections can be prevented.

All patients should be reviewed within 72 hours to assess their response to treatment. If a woman has persistent symptoms and signs an alternative diagnosis or change in antibiotic therapy may be indicated. Further follow up two to four weeks later is recommended to check that patients have completed their antibiotics and that sexual partner/s have been tested and treated. The importance of avoiding further infections should also be reiterated.

2.4.3 Improving diagnosis and management

Evidence from a range of settings and countries shows that there is capacity for improvements in PID diagnosis and management. In the UK, a survey of general practitioners (GPs) found that only a third correctly named two signs and two symptoms of PID, a fifth

reported that they usually treated sexual partner/s and 54% named the correct antibiotic therapy.[217] Other UK studies have found that 34% of women diagnosed with PID in general practice received the correct antibiotic treatment[218] and in sexual health clinics that PID diagnostic acumen differed with clinician experience.[45] In the US, analyses of emergency department data have shown that around a third of diagnosed PID cases received antibiotic treatment that was consistent with Centers for Disease Control (CDC) guidelines.[219-221] In Australia, a clinical audit of records in remote primary health services found that PID was only diagnosed in 11% occasions in which PID symptoms were recorded and was inadequately treated if diagnosed.[48] Another clinical audit in an Australian sexual health clinic found disparate PID diagnostic practices between experienced doctors.[44]

Strategies to improve PID diagnosis and management have been infrequently reported, and where reported have been largely based in US hospital or outpatient settings and shown moderate success. In paediatric outpatients, a multi-level intervention targeting clinicians (treatment algorithm, practice guideline, training) and patients (take home antibiotics, written instructions) was followed by a substantial increase in the proportion of PID patients receiving an appropriate PID medication (38% at baseline vs 91% postintervention) and in patients attending for follow up within 72 hours (10% at baseline vs 43% postintervention).[222] In hospital emergency departments and adolescent clinics, an RCT compared the addition of an educational PID selfcare video (targeting patients) to standard care to standard care only. The study reported that overall follow up rates at 72 hours were low (24%) but were higher for interventions than controls (32% vs. 16%) on univariable analysis. There was no difference in medication compliance between intervention and control participants, but sexual partners of those viewing the video were more likely (AOR 3.1; 1.0, 9.4) to be treated than partners in the control group.[223] Another RCT assessed the impact of a short teaching tool using hypothetical scenarios on PID knowledge for emergency department clinicians, and although overall PID knowledge was low, clinicians who received the intervention had higher knowledge about PID treatment but not about PID diagnosis.[46] Another multifaceted intervention in a US emergency department targeted medical and nursing staff (educational presentations, posters of PID treatment guidelines) and patients (written discharge handout) and showed improvements in PID diagnosis, PID treatment, and, sexual history taking for

young women presenting with lower abdominal pain.[47] Targeting doctors and nurses was viewed as critical to the interventions success.

A 2012 systematic review[224] assessed three of these studies,[46 222 223] and noted that the findings were not generalisable to primary care settings where most mild to moderate PID is diagnosed and managed. Further research recommendations were for investigations that measured whether interventions such as shortened clinical management guidelines or simplified antibiotic regimens lead to improvements in PID diagnosis and management compared to current practice, particularly in primary care settings where there is capacity for improvement. Education and training has been a component of successful multifaceted PID focussed interventions.[47]

Future implementation of evidence based resources toward improving PID diagnosis and management should be complemented by professional support and training for clinicians in a range of health settings where women with recent lower abdominal pain may present.[21 45] Low abdominal pain is often the key reason for a woman's presentation to a clinical setting and for clinicians to consider a PID diagnosis. Resources that provide decision trees for assessment of recent onset low abdominal in women of reproductive age and possible differential diagnoses have been developed[199] and could be a tool in workforce training. There is a need for an evidence base for such resources.

2.5 PID epidemiology

PID and its sequelae account for substantial health care costs[20] and their prevention, in particular infertility, is an important reason for STI control policies.[21 22] Many developed countries have introduced programs for opportunistic chlamydia testing[23 24] and the UK has implemented systematic chlamydia screening for young sexually active persons.[25] In consideration that outcomes such as infertility may not be recognised until affected women try to conceive, PID has been used as an interim outcome for monitoring the relationship between STIs and more distant adverse outcomes.[22]

Measuring the epidemiology of PID including its distribution, determinants and outcomes of PID is challenging. These challenges stem from the fact that PID diagnosis is inaccurate, the microbial aetiology of many PID cases is unknown, [19] and, that depending on clinical severity, women with PID will be represented in data from a range of health settings. For example,

mild to moderate PID is often treated on an ambulatory basis in primary care clinics or hospital emergency departments and severe PID is often treated on an inpatient basis.[1 6 29 30 31 32] Further, PID is generally not a notifiable disease, few countries have systems for PID surveillance, and, measurement of PID trends relies largely on ecological analyses of routinely collected data from health settings where PID cases are diagnosed. These include hospitalisations, ambulatory care and infertility data, that may also be complemented by STI surveillance data to provide a context of STI trends in a population, and, other clinical data for example STI testing data to provide a measure of STI control responses.

An underlying limitation of any study of PID epidemiology using routinely collected data is the uncertainty around PID diagnosis and that it is virtually impossible to assess the validity and reliability of this diagnosis. Another important limitation is that such studies will only reflect women with PID who have presented to a clinical setting and who have had PID diagnosed, therefore not representing sub-clinical PID cases that are still at risk of progressing to tubal damage and infertility.

2.5.1 PID incidence and prevalence

During the 1960's and through to the 1980's, the gonorrhoea epidemics in some high-income countries were associated with increasing rates of PID and followed by increasing ectopic pregnancy rates.[4 15 225 226] In England and Wales, hospital admission rates in which PID (acute or chronic) was the main reason for admission increased between 1966 and 1985 to a high of 132 per 100,000 women aged 15-44 years, with the highest increases seen for women aged 15-24 years and around two-thirds of admissions being for acute PID (Figure **3**).[4 15 225] Subsequent declines in PID admission rates during the 1990s for England and Wales were paralleled by increasing PID diagnoses in general practice suggesting a shift to management in primary care.[4] Also in Sweden, increasing hospital admissions rates for PID during the 1970s closely followed high gonorrhoea rates peaking at 11 cases per 1000 women aged 15-39 years in 1974 then declining in the late 1970s to 1980s.[227]

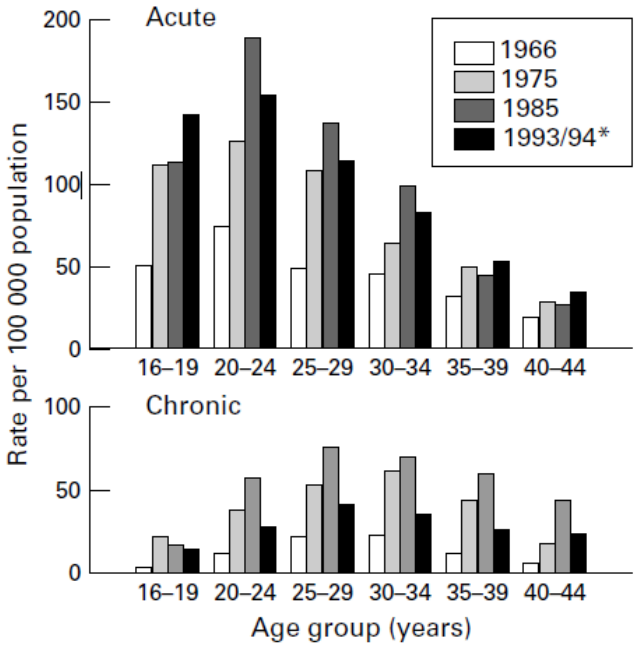

Figure 3 Pelvic inflammatory disease by age group, hospital inpatients England and Wales: 1966–1993/94.

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Figure 3 PID by age group, hospital inpatients England and Wales, 1966-1993/94

Starting in the 1980s and 1990s, widespread declines in rates of PID hospitalisation have been reported for many developed countries that have continued into the 2000s, and, have also been found to coincide with declines in primary care rates of PID.[14 24 42 43 228-230] Some instances of increasing PID rates have been reported, for example between 2005 and 2008 among 15-24 year old women in the north of New Zealand.[184] Admission rates vary widely between countries. One study assessing PID trends for the period 1998-2008 across Sweden, Denmark, New Zealand and Australia reported PID admission rates that ranged from 37 to 194 cases per 100,000 women aged 15-39 years during the 2000s. Australian PID admission rates were 89 per 100,000 in 2007.[24] In the US, PID admission rates were 140 per 100,000 in 2001 for women aged 15-44 years.[42] A recent commissioned review on sexually transmitted diseases presented hospital discharge rates during 1990-2014 for inflammatory diseases of female pelvic organs (including PID from any cause) for 13 countries across Europe, America and Australia that showed wide variability between countries and general declines to around 2007 that then appeared to plateau in several countries including Australia (Figure **4**).[115]

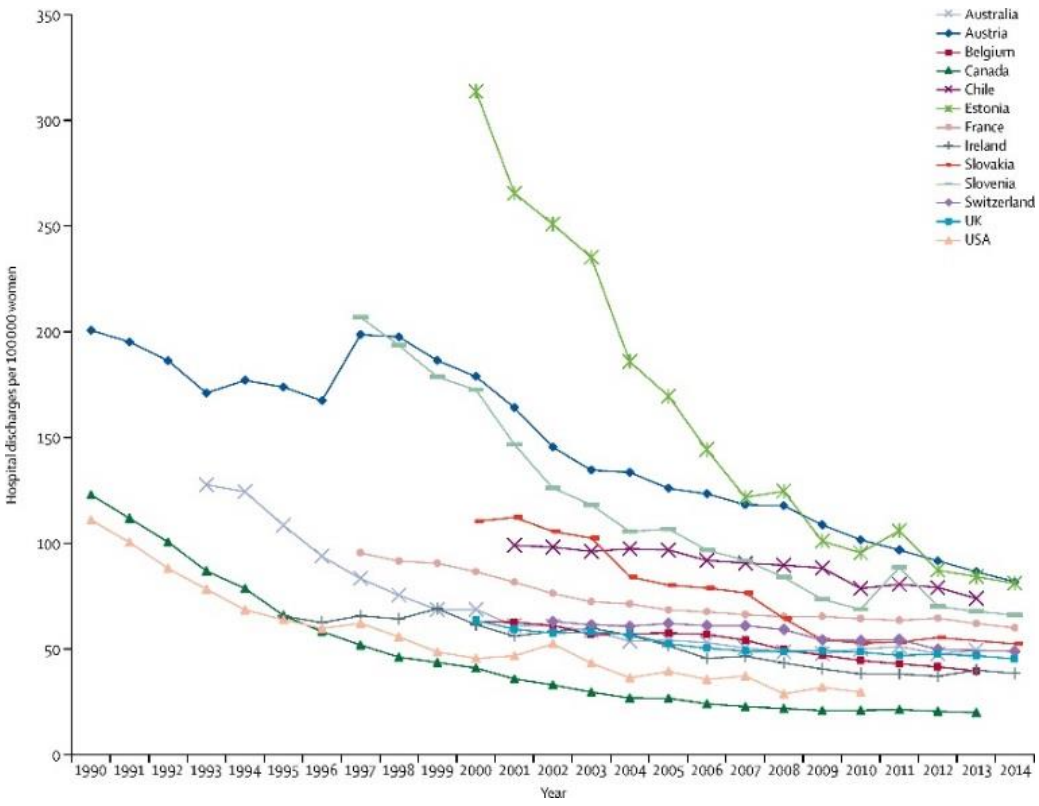

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Figure 4 Hospital discharge rates for inflammatory disease in female organs

Trends in PID rates are difficult to interpret and comparisons between countries are problematic because of differences in healthcare systems, diagnosis and coding, and the underlying prevalence of PID risk factors. Declining hospitalisations have been observed in association with increasing chlamydia diagnoses and testing, that might appear to be influenced by STI control measures. However, similar declining trends in PID have been observed in high and low chlamydia testing countries.[23 24 115] Changing sexual behaviours in response to the HIV epidemic have also been hypothesised to have contributed to falls in STI and PID rates.[229] The PEACH study showed similar outcomes following treatment of mild to moderate PID in outpatient compared to inpatient settings.[100] It is possible that declines in inpatient PID represent a shift in care to ambulatory settings, however declines in admission and ambulatory care rates have been reported over similar periods.[42 187 228] Several studies have shown that PID is diagnosed and managed more frequently in ambulatory care than hospital settings, with admitted cases more likely to be severe than those managed in primary care. In the UK, PID was diagnosed in 1.7% of general practice encounters for reproductive

aged women, and, was extrapolated to represent 165,000 PID cases compared with 21,168 inpatient and 5735 in genitourinary medicine clinics in the same year - 1992.[186] More recently in the UK, declining rates of definite / probable PID among reproductive age women attending general practice between 2000 and 2011 were reported. However, on inclusion of possible PID cases, rates increased, highlighting the difficulties in diagnostic coding for PID and the impact this may have on PID trends.[231] Another study based in the US showed that of almost 770,000 PID cases diagnosed annually between 1995 and 2001, that 91% were diagnosed in ambulatory care. Hence highlighting the importance of ambulatory care settings for measurement of the PID incidence and for a focus on optimal management of PID where the majority of cases are diagnosed and treated.[42]

2.5.2 Australian context

In Australia, chlamydia is the most commonly notified STI and is diagnosed predominantly among young heterosexuals. Surveillance data have shown steady increases in chlamydia notification rates between 2007 and 2011 (largely due to increased testing) that remained stable between 2011 and 2015 then increased again in 2016 and 2017. Around 100,000 chlamydia cases were notified to Australian Departments of Health in 2017, 73% were in the 15-29 year age group.[33-35] Gonorrhoea infection is predominantly diagnosed among MSM and heterosexuals in remote Aboriginal communities, but notification rates in women have more than doubled from 2007-2017, reaching a total of 7282 cases among women in 2017, and the greatest change being in women in urban areas. [33-35] Australian surveillance data also monitor trends in chlamydia and gonorrhoea testing. Medicare is the Australian Government funded universal health care system.[232] Between 2012 and 2016, the number of Medicare-rebated chlamydia and gonorrhoea tests in Australia increased by 35% and 64% respectively. Although rates of chlamydia and gonorrhoea diagnoses will be influenced by testing patterns, analyses of Medicare testing data suggests that recent increase in gonorrhoea notifications may be related more to increased transmission and less to increased testing,[35] raising concerns about potential adverse reproductive impacts for women.

Care for most STI cases and PID is provided through primary healthcare services that include general practice, Aboriginal community controlled health services, sexual health and family planning clinics. In Australia, individuals are able to attend multiple general practice clinics of

their choice and are not registered to any one GP.[233] General practices are privately owned businesses where the costs for an individual's visit are partially or fully covered by Medicare or by other practice incentive schemes.[234] General practices are widely available, although there are fewer clinics in rural areas than the city.[235] Sexual health clinics are less widely available than general practice clinics but are publicly funded and provide testing and care for large numbers of complex patients or priority populations as well as professional development, clinical advice and research.[21] Hospitals in Australia include a mix of public (government-funded) and private hospitals,[236] with public hospital emergency departments providing emergency care.[237]

Like many other countries, Australia does not have a system for surveillance or routine monitoring of PID trends, and, analyses presenting trends for PID and other STI sequelae are infrequent. Two studies have assessed trends in PID hospitalisation rates for the Australian state of NSW; showing declining rates per 100,000 15-34 year old women from 165 in 1992 to 64 in 2001,[14] and declining rates per 100,000 15-29 year old women from 58 in 2001 to 44 in 2010.[238] These declines were paralleled by declining ectopic pregnancy hospitalisation rates (2001-2008)[239] and were in contrast to increasing chlamydia notification rates[14] over a similar period. A cross-country analysis presented PID rates for Australia and for other high-income countries that have health care systems with universal access. As noted above, Australian PID admission rates for women aged 15-39 years were 89 per 100,000 in 2007.[24] The one study assessing PID trends in Australian primary care, presented data for 1998 to 2003 and reported that PID diagnosis rates for 15-34 year old women declined from 39 to 19 per 10,000 patient encounters.[228]

As noted above, interpretation of these trends is difficult and updated data for Australia are needed. The declines in rates of PID diagnosed in admissions and primary care during the 1990s and 2000s could reflect STI trends at that time. Gonorrhoeal PID can be more clinically severe than chlamydial PID. Australian data have shown the risk of PID hospitalisation was substantially higher following a gonorrhoea infection than a chlamydia infection, although the risk of hospitalisation was higher following gonorrhoea or chlamydia compared to no infection.[40 41] These declines in PID hospitalisations occurred in a period that gonorrhoea diagnoses for Australian women were rare, potentially resulting in less severe PID cases

requiring hospitalisation. Results from the PEACH study around this time provided evidence for management of mild-moderate PID in outpatient settings, hence declining hospital rates may also reflect altered treatment regimens.[100] Chlamydial PID can be more indolent in nature and while it is possible that increased testing coverage led to earlier diagnosis of some chlamydia infections thereby limiting progression to PID, it is also possible that there is a large reservoir of chlamydial PID that is not diagnosed in the primary care setting. As noted earlier, study of PID rates in UK primary care clinics found that rates of definite and probable PID declined between 2000 to 2011, but on inclusion of possible PID case the study found that rates increased.[231]

2.6 The sequelae of PID

PID can lead to several long-term complications that can have debilitating and severe impacts. The most common is chronic pelvic pain, thought to be due to pelvic adhesions, and defined as low abdominal pain lasting at least six months and causing functional disability or requiring treatment. Although chronic pelvic pain has other causes (e.g. endometriosis), PID is one of the more common gynaecologic conditions reported by women also reporting chronic pelvic pain.[240] Following PID treatment, 18% of a cohort of Swedish women[5] and over a third of women in the PEACH study[121 241] experienced chronic pelvic pain. A data linkage study in the UK followed women who have been hospitalised for PID, finding they were 10 times more likely to be admitted for abdominal pain than women admitted for other reasons.[242] Previous PID episodes appear to increase a woman's risk of chronic pelvic pain after PID and a range of demographic, clinical and behavioural risk factors have been identified.[241] The impacts of chronic pelvic pain after PID are severe, with affected women reporting reduced physical and mental health compared to women without chronic pelvic pain.[243]

Infertility or ectopic pregnancy that occur due to fallopian tube scarring are the other serious sequelae of PID. Infertility, is defined as when a sexually active woman who is not using contraception does not conceive after 12 months.[244] Ectopic pregnancy is when a fertilised egg implants outside of the uterus, most commonly in the fallopian tubes.[245] The relationship between PID, tubal infertility and ectopic pregnancy has long been recognised. However, quantifying the relationship between PID and these outcomes is difficult because of the non-

specific nature of a PID diagnosis and the long follow up timeframes necessary to measure these outcomes.

The Lund cohort study followed 2501 women with clinically suspected PID during the 1960s to 1980s, and found that 16% of women with salpingitis diagnosed by laparoscope developed infertility compared with 2.7% of women without salpingitis.[5] Furthermore, a higher ectopic pregnancy rate among first pregnancies was found for women with PID compared to those without. The PEACH study provides further evidence for these relationships. During the 1990s a total of 831 women aged 14-38 years were randomised to inpatient or outpatient treatment for mild to moderate PID in the USA and followed for up for 84 months. Over a mean of 35 months, 21% of women experienced recurrent PID episodes, 19% were infertile, <1% experienced an ectopic pregnancy, and over a third experienced chronic pelvic pain. The risk of infertility was higher for women experiencing repeated episodes of PID.[246 247]

2.7 STI control and PID

2.7.1 Overview

Because PID is largely of STI aetiology, its control is largely considered in the context of STI epidemiology and control. STI control strategies, particularly for chlamydia are often rationalised by the need to reduce PID incidence and other complications with screening debated as an intervention toward this objective. The rationale being that screening will diagnose asymptomatic chlamydia infections that then can be treated and in turn reduce progression of chlamydia infections to PID.

There were an estimated 357 million new cases of curable STIs worldwide in 2012, including 131 million cases of chlamydia, and 78 million cases of gonorrhoea. These and other STIs adversely impact the health and lives of children, adolescents and adults around the world, and a global response is a priority.[139]

Addressing STIs requires a coordinated and sustained approach that seeks to reduce incidence and prevalence of STIs and their associated morbidities. A mix of primary and secondary prevention activities, and, systems for monitoring and evaluation are all essential to a coordinated response across the continuum of care (Figure **5**).[139] The shape of any

response and the STIs that are prioritised will vary between countries depending on the epidemiological and social context, priority populations, and, availability and quality of health and preventive services. The World Health Organisation in its Global Health Sector Strategy on STIs 2016-21 has provided targets around reductions in gonorrhoea and syphilis, but not chlamydia because the optimal means to control chlamydia are not known.[139] However, in view of the high frequency of chlamydia infections in Australia and that asymptomatic infections can ascend to the female upper genital tract to cause complications[115 248 249] this section will largely focus on chlamydia control, with some focus on other infections (particularly gonorrhoea*)* that are relevant to PID and other adverse reproductive tract complications.

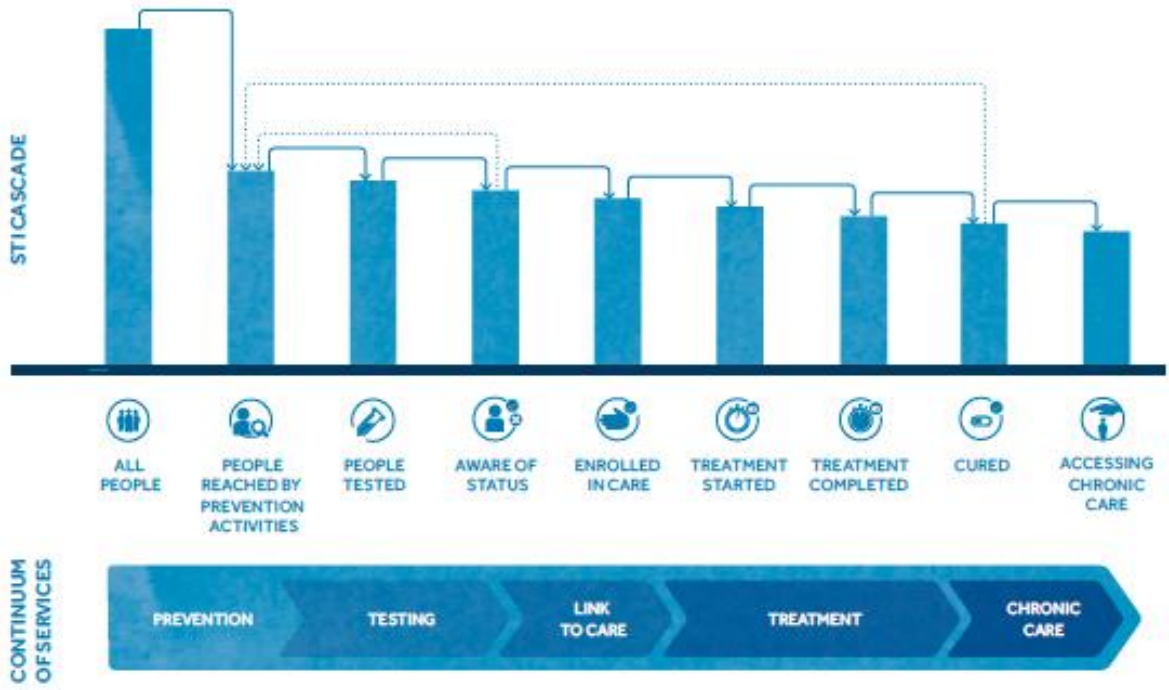

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Figure 5 The continuum of sexually transmitted infection services and the cascade

Primary prevention underlies STI control. It comprises activities that aim to promote safer sexual behaviours that leads to a reduction in the risk of acquiring an STI. Primary prevention activities include promotion of safer sex behaviours, consistent and effective condom use, access to condoms, and STI related knowledge, that can directly target at-risk individuals such

as advice in a healthcare setting, or populations such as through school sexual health education or social marketing media campaigns.[21 248 250] Primary prevention activities that prevent chlamydia will in general be effective in preventing other STIs.

Secondary prevention comprises case detection and effective case management for people who already have an infection. Some people will have symptomatic infection that is diagnosed when they present to a healthcare setting and are tested. Other people will have asymptomatic infection that is identified when they are tested for reasons such as they are a sexual partner of someone with a diagnosed STI, or because they are identified as being at high risk for infection (Figure **6**).[115] Testing of asymptomatic persons can be opportunistic when a test is offered to asymptomatic people in known risk groups (such as young age, reports male to male sex), or, through a screening programme where a defined subpopulation considered at increased risk of infection compared to the general population are regularly offered testing.[248] Case management includes treatment of all diagnosed cases of STIs with an effective antimicrobial regime, notification and treatment of sexual partners to prevent onward transmission, and potential reinfection or complications, and re-testing to identify and treat repeat infections. These activities should be supported by systems for monitoring and evaluation of their uptake and impact and systems for monitoring antimicrobial resistance, particularly *Neisseria gonorrhoeae*.

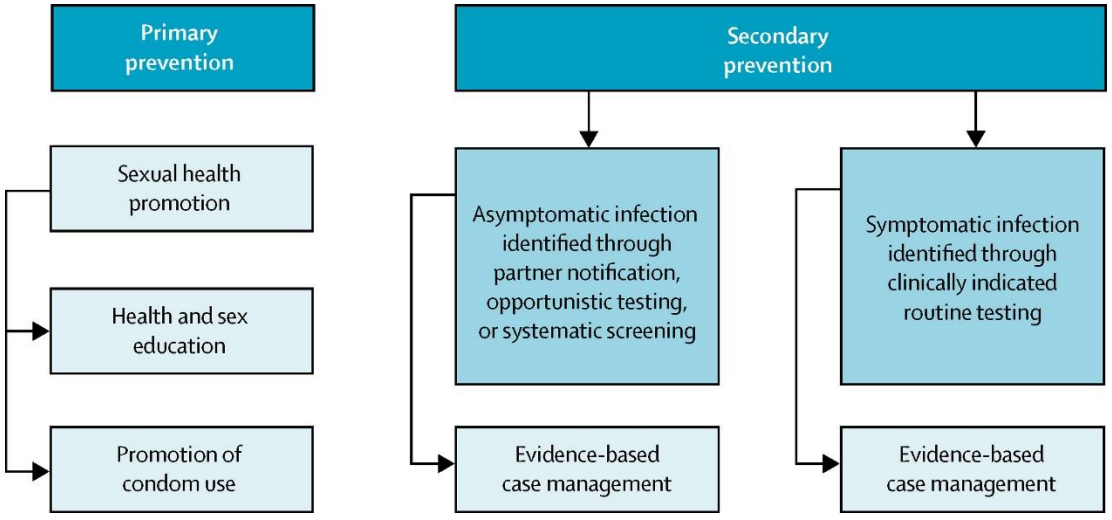

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Figure 6 Interventions for the control of chlamydia in a population

For chlamydia, several high-income countries have recommended yearly opportunistic testing for young sexually active heterosexual women and men with corresponding increases in testing and case detection reported.[13 23 24 37 251 252] The UK has implemented a national chlamydia screening programme for young sexually active persons. Chlamydia screening trials have been conducted in Denmark, England, the Netherlands, the US and most recently in Australia[39 130 131 253-256] in which PID has been used as an outcome measure. These trials have been conducted amid worldwide debate as to whether chlamydia screening is cost-effective in terms of reducing chlamydia transmission and PID incidence.[257] Chlamydia testing programs – both opportunistic or screening – could prevent PID either indirectly if they lead to decreased chlamydia prevalance or directly if chlamydia is detected and treated before PID develops. Thereby, the success of direct PID prevention will depend on how long it takes for a chlamydia infection to ascend to the upper genital tract,[258] which can be within days or weeks.[259] Further, there is no lasting immunity to chlamydia infection and there are concerns that increased testing and treatment could render more people at risk of reinfection and thereby increase the risk of PID at population level.[260 261]

Lower PID incidence rates have been reported over one year following a single offer of a chlamydia test compared to no test when results were pooled in a systematic review.[262] However this reduced risk was less apparent in studies at lower risk of bias[39 255] than in other studies.[130 131] In the Netherlands, a trial of register based chlamydia testing via annual postal invitations achieved an initial participation rate of 16% that declined with each invitation.[253] In view of the low uptake and findings of no difference in chlamydia positivity between intervention and control areas, ongoing implementation of the program was not recommended.[253] The POPI study in the UK found that most PID occurred in women who tested negative for chlamydia at baseline, suggesting these PID cases were related to incident infection and that a single yearly screen might only prevent a small amount of PID.[39] Further analysis of the POPI data estimated the costs of chlamydia screening for women aged 16-24 years and living in London during 2009 to be around £4 million to prevent around 400 cases of PID that incurred £64,000 in healthcare costs.[263] Most recently, the Australian Chlamydia Control Effectiveness Pilot (ACCEPt) trial investigating the effect of annual offers of chlamydia testing in general practice has concluded,[256] and found no evidence to support a reduction in chlamydia prevalence associated with the intervention or in rates of PID diagnosed in general

practice. However, ACCEPt did find that PID hospitalisation rates were significantly lower in intervention than control clusters (24.2 per 10 000 women versus 37.9 per 10 000 women), difference (-13.7 per 10 000; 95%CI -26.9, -0.5; aRR 0.6, 95%CI 0.4, 1.0).[256]

Although it is likely that chlamydia screening does reduce PID, it is unlikely to be cost-effective and the focus of many discussions on chlamydia and STI control is shifting from widespread testing to primary prevention and to strengthening case management to prioritise partner notification and timely re-testing after treatment to prevent or detect re-infections earlier and to reduce complications.[115 248]

2.7.2 Australian context

Recent STI control policies in Australia have had a strong focus on opportunistic testing with objectives to detect and treat asymptomatic infections, reduce onward transmission and reduce associated morbidities, including PID.[21 36 250] Like other high-income countries yearly opportunistic chlamydia testing is recommended for young sexually active heterosexual women and men. Annual or more frequent STI testing for chlamydia, gonorrhoea and syphilis in groups considered to be high risk, for example asymptomatic MSM reporting high risk sexual behaviours[37 38] also forms a significant component of Australia's STI control policy.[21] From around 2012, most Australian laboratories have conducted dual chlamydia and gonorrhoea testing, in which both tests are automatically performed when a test for either chlamydia or gonorrhoea is ordered.[35]

Increases in testing have been accompanied by increasing chlamydia diagnoses, although recent modelling reported in Australian surveillance reports suggest that less than half of new chlamydia infections were diagnosed among 15-29-year-olds in 2016 and around a third of people diagnosed with chlamydia are re-tested within six months.[34] Increases in gonorrhoea testing and diagnoses have also occurred with recent data indicating that heterosexual transmission of gonorrhoea transmission is increasing.[34] Further, as noted above (Section 2.7.1) the ACCEPt study found it was not possible to reduce chlamydia prevalence in the population with achievable levels of annual testing. The ACCEPt study also showed sub-optimal rates of partner notification and retesting after chlamydia treatment.[256 264] Other Australian evidence shows high rates of repeat chlamydia diagnosis in the year after treatment.[265]

The need for improved case management is identified in Australian policy. A range of interventions to improve partner notification (e.g. partner notification websites)[266] and retesting (e.g. SMS reminders and mailed specimen kits)[267] have been evaluated, however mild to moderatetheir widespread uptake is irregular. Priority actions include improving access to sexual health care via a strengthened primary care sector, development of methods to enhance partner notification and treatment, and, methods to increase re-testing after treatment to detect repeat infections early.[21 250]

Australian policy identifies PID, and, also ectopic pregnancy and infertility as important STI associated morbidities. Interventions that aim to increase partner notification or uptake of re-testing are recommended for their potential to reduce transmission, reinfections and complications. However, Australia has no system for monitoring STI-related morbidities and a need to develop appropriate indicators has been identified.[21 250]

Chapter 3: Population attributable fraction of PID associated with chlamydia and gonorrhoea

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3.1 Introduction

This Chapter and Chapter 4 address the first objective of this thesis, to investigate the microbial associations with PID in Australia. Chlamydia and gonorrhoea infections are well-known PID causes, and, PID prevention is a key objective of opportunistic testing or screening for these infections.[21 22] It is important to know the attribution of these STIs to PID to ascertain the potential impact of control activities on this morbidity. Further, country and risk group specific estimates are needed to reflect the underlying prevalence of STIs and other risk factors. A case control study among Australian sexual clinic attendees between 2002 and 2006 identified chlamydia in 19.5% women with a PID diagnosis.[44] Aside from two data linkage studies showing that chlamydia or gonorrhoea conferred a higher risk of PID hospitalisation than no infection[40 41] there are no recent Australian data about PID pathogens.

This Chapter presents findings from an analysis of routinely collected Australian sexual health clinic data. This analysis was published in *Sexually Transmitted Infections*[268] and presents findings for the first estimates based on clinical data of the PAF of chlamydia and gonorrhoea for their contribution to PID in Australia. The PAF takes into consideration both the population prevalence of an exposure and the magnitude of the risk of an outcome that is associated with the exposure. The PAF is a measure that can be used by policy makers to consider the potential benefits of an intervention. For example, if chlamydia screening were introduced and if chlamydia was eliminated, then, how much PID in the population may be avoidable. Individual-level risk factors for a PID diagnosis were also assessed. The methods

used in this chapter are detailed in the following publication. Multivariable logistic regression models were used to adjust individual level and population level estimates for demographic and behavioural factors identified a priori as confounders on the causal pathway between chlamydia and gonorrhoea infection and PID. Further, because not all women attending the clinic were tested for chlamydia or gonorrhoea, a sensitivity analysis using multiple imputations for missing test result was conducted. The findings for the sensitivity analysis were published as additional material that was published online only and are provided in Appendix 1.

ORIGINAL ARTICLE

Population attributable fraction of pelvic inflammatory disease associated with chlamydia and gonorrhoea: a cross-sectional analysis of Australian sexual health clinic data

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ABSTRACT

Objectives Pelvic inflammatory disease (PID) is an important cause of female infertility and can occur when micro-organisms such as chlamydia or gonorrhoea ascend to the upper genital tract. PID has been used as an outcome measure in chlamydia screening trials; however, few data have quantified the PID burden that could be avoided by preventing chlamydia. We estimated the population attributable fraction (PAF) of PID associated with a current chlamydia or gonorrhoea infection among females 16–49 years attending an Australian sexual health clinic (SHC) (2006–2013).

Methods Using multivariable logistic regression, PAF estimates were adjusted for age and behavioural factors. Two separate analyses were undertaken: one among 'chlamydia-tested' women and one among a subset of chlamydia-tested women who were also tested for gonorrhoea ('chlamydia+gonorrhoea-tested'). A sensitivity analysis using multiple imputation was conducted to assess the impact of missing data on results.

Results Among 15 690 chlamydia-tested women, 1279 (8.2%, 95% CI 7.7% to 8.6%) were chlamydia positive, 436 (2.8%, 95% CI 2.5% to 3.0%) had PID diagnosed and the adjusted PAF for chlamydia was 14.1% (95% CI 9.9% to 18.0%). Among the chlamydia +gonorrhoea-tested subset (n=8839), 681 (7.7%, 95% CI 7.2% to 8.3%) tested positive for chlamydia only, 30 (0.3%, 95% CI 0.2% to 0.5%) for gonorrhoea only, 22 (0.2%, 95% CI 0.2% to 0.4%) for chlamydia and gonorrhoea and 419 (4.7%, 95% CI 4.3% to 5.2%) had PID diagnosed. The adjusted PAF was highest for chlamydia only (12.4%, 95% CI 8.4% to 16.2%) compared with gonorrhoea only (0.9%, 95% CI −0.1% to 1.8%) or concurrent infections (1.0%, 95% CI 0.0% to 1.9%).

Conclusions In this high chlamydia prevalence SHC population, eliminating a current chlamydia infection might at most reduce PID by about 14%.

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BACKGROUND

Pelvic inflammatory disease (PID) is an important cause of tubal factor infertility and ectopic pregnancy.[1] Occurring when pathogens ascend to the upper genital tract, PID often follows the sexually transmitted infections (STIs) *Chlamydia trachomatis* (chlamydia) and *Neisseria gonorrhoeae* (gonorrhoea) with a causal role for *Mycoplasma genitalium* (MG) established[2] and bacterial vaginosis (BV) also considered a factor.[3]

Past studies have cultured chlamydia or gonorrhoea from the cervix of 29% and 26%, respectively (estimates vary), of acute PID cases.[1] More recently, nuclear acid amplification tests have detected these infections in 17% PID cases.[4] Largely affecting young heterosexuals, chlamydia is the most commonly diagnosed bacterial STI throughout the developed world with all age rates per 100 000 of 359 in Australia,[5] 447 in the USA[6] and 386 in the UK.[7] Gonorrhoea is more common via male-to-male transmission in many countries, with all age rates per 100 000 of 65 in Australia and 55 in the UK compared with 106 in the USA where rates are high among young heterosexuals.[5–7] Estimates of the risk of PID from chlamydia or gonorrhoea vary, and there are questions about the natural history of these infections. PID may develop in 2%–5% of untreated chlamydia infections over 2 weeks,[8] and 10% over 1 year.[9] Although hampered by methodological or sample size issues, other evidence suggests up to 30% chlamydia infections could develop into PID.[10] PID has been diagnosed in 13% of chlamydia-infected or gonorrhoea-infected adolescents in the 7–15 days between testing and treatment[11] and modelling suggests 4%–7% gonorrhoea infections may develop into PID over 6–12 months.[12]

PID prevention is a key objective of STI screening or opportunistic testing.[13 14] It is important to determine the attribution of STIs and other PID risk factors in a population to understand the potential impact of control activities on this morbidity. Population attributable fraction (PAF) considers both magnitude of risk of an outcome (such as PID) associated with an exposure (such as chlamydia) and the exposure's population prevalence,[15] and could provide a measure of PID burden that might be avoided by preventing PID risk factors. Given that risk factor prevalence and their contribution to PID will vary between populations, the PAF for PID is likely to differ between risk groups, countries and settings. For example, the STI-associated PAF for PID might be higher in sexual-health-clinic (SHC) attendees than in the general population.

Our aim was to estimate the potentially avoidable PID burden if chlamydia or gonorrhoea were

eliminated from the population. We report population-level and individual-level risks associated with PID and a current chlamydia or gonorrhoea infection in female SHC attendees.

METHODS

Setting and study population

We conducted a cross-sectional analysis of routinely collected data from female patients 16–49 years during their first episode of care (first and follow-up visits in the next 30 days) at a large Australian SHC between January 2006 and June 2013. Current sex-workers were excluded.

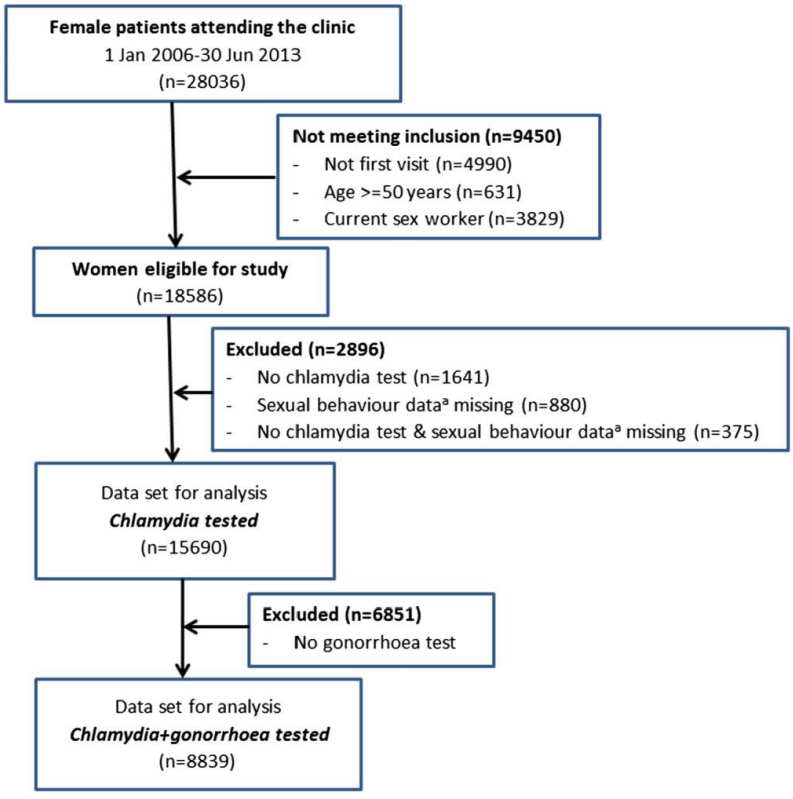
Melbourne Sexual Health Centre (MSHC) is the major public SHC in the state of Victoria, Australia, and provides a free triage-based walk-in service. Attendees at higher sexual risk, with symptoms suggesting an STI, or females with pelvic pain are triaged in. Details of attendees triaged out of MSHC are not collected; however, over 85% of all attendees are triaged in. All new female patients are offered a chlamydia test. The decision to conduct gonorrhoea, MG or BV tests depends on the clinician's assessment and the patient's clinical presentation and sexual history. During the study, a total of 28 036 women were seen in MSHC and 18 586 (66%) met the inclusion criteria (figure 1): 55% were asymptomatic, 89.1% were tested for chlamydia, 50.5% for gonorrhoea, 39.1% for BV and 8.1% for MG. This analysis was limited to investigating chlamydia and gonorrhoea as the most common bacterial STIs tested and the focus of national testing recommendations.[16]

Primary outcome and exposure definition

The primary outcome was PID. The primary exposure was a current genital chlamydia or gonorrhoea infection. Clinical PID diagnosis was guided by Centers for Disease Control and Prevention criteria that include uterine tenderness, cervical motion tenderness or adnexal tenderness in sexually active women with pelvic pain and also signs of cervicitis or abundant vaginal leukocytes.[13] Chlamydia and gonorrhoea diagnoses were based on laboratory results: (i) chlamydia on strand displacement amplification from urine, high vaginal swabs (HVS) and cervical swabs; (ii) gonorrhoea on HVS and cervical swab culture. Test results for MG (urine, HVS and cervical swab PCR) and BV (Nugent's score of 7–10 or 4–6 with clue-cells)[17] were collected for PID cases.

Data collection and exclusions

Information on demographics, sexual behaviour (condom use, number of male sexual partners (MSPs)), current contraception (intrauterine device (IUD), hormonal), laboratory results and clinical diagnosis (including PID) were extracted from the computerised medical record. Self-reported symptoms (such as pain, vaginal discharge, intermenstrual bleeding, genital lesions) were recorded at triage. A binary 'symptoms at triage' variable was created. Behavioural data were self-entered by patient/s and diagnoses by clinician/s. Records without behavioural information were excluded. Because not all women were chlamydia and gonorrhoea tested, two datasets were prepared (figure 1): (1)



a. Number of male partners and condom use with male partners in the last 3 and 12 months

Figure 1 Flowchart of participants in the chlamydia-tested and chlamydia+gonorrhoea-tested datasets.

comprised all women tested for chlamydia ('chlamydia-tested') (n=15 690); (2) a subset of chlamydia-tested who were also tested for gonorrhoea ('chlamydia+gonorrhoea-tested') (n=8839).

Statistical analysis

Data were analysed using STATA statistical software V.13.0. The PID prevalence and 95% CIs were calculated. For each dataset, the population-level and individual-level risk associated between a current chlamydia or gonorrhoea infection and PID were investigated using univariable and multivariable logistic regression. Age, country of birth, number of MSPs (past 3, 12 months), condom use (consistent, inconsistent, no MSP/vaginal sex, past 3, 12 months) and contraception method were identified a priori as potential confounders. We investigated whether age modified the association between chlamydia or gonorrhoea and PID by comparing logistic regression models with and without an interaction term between age and chlamydia or gonorrhoea using the likelihood ratio test. No effect modification was found. To assess the impact of missing data we conducted a sensitivity analysis using multiple imputation[18] and compared the estimated OR from the complete-case analyses with those derived from multiple imputation. Online supplementary tables S1 and S2 provide details of the imputation model. We calculated the PAF of PID associated with chlamydia and/or gonorrhoea infection from the PID prevalence and OR estimates from the complete-case analyses for both datasets. Under the assumptions of causality and low PID prevalence, the PAF formula for cross-sectional analyses is:

$$\mathrm{PAF} = 1 - \frac{\sum_{i=1}^{n} \mathrm{pexp}_i}{\sum_{i=1}^{n} \mathrm{p}_i}$$

where n is the sample size, pexp_i is the predicted probability for the ith individual from the multivariable logistic model which included the exposure and p_i is the predicted probability for the ith individual from the multivariable logistic model without the exposure variable.[15] Because symptoms may prompt patients to seek medical care and be STI-tested, we undertook a subgroup analysis based on the 'symptoms at triage' variable to assess whether the PAF of PID associated with chlamydia or gonorrhoea varied between women reporting and not reporting symptoms at triage.

The Alfred Health Human Ethics Committee (EC00315) granted ethical approval (322/13).

RESULTS

Participants and PID cases

Between 2006 and 2013, 18 586 new female patients were seen in MSHC: 15 690 comprised the chlamydia-tested group among whom 1279 (8.2%, 95% CI 7.7% to 8.6%) were chlamydia positive and 436 (2.8%, 95% CI 2.5% to 3.0%) had PID diagnosed. Of these 436 PID cases, 94 (21.6%) were chlamydia-associated, of which 66 (70%) were co-diagnosed with PID and chlamydia at first visit and 28 (30%) were diagnosed with PID within the next 3–28 (median 7) days. The chlamydia+gonorrhoea-tested subset comprised 8839 women; 681 (7.7%, 95% CI 7.2% to 8.3%) tested positive for chlamydia alone, 30 (0.3%, 95% CI 0.2% to 0.5%) for gonorrhoea alone, 22 (0.2%, 95% CI 0.2% to 0.4%) for both gonorrhoea and chlamydia and 419 (4.7%, 95% CI 4.3% to 5.2%) had PID diagnosed. Of these 419 PID cases, 1.2% (95% CI 0.4% to 2.8%) were diagnosed with chlamydia+gonorrhoea co-infection, 19.6% (95% CI 15.9% to 23.7%) with chlamydia alone and 1.2% (95% CI 0.4% to 2.8%) with gonorrhoea alone. MG was detected in 2.9% (95% CI 1.5% to 4.9%) of PID cases, BV in 15.5% (95% CI 12.1% to 19.3%) and no pathogen in 61% (95% CI 55.8% to 65.3%). Table 1 provides the characteristics and PID prevalence for both datasets. Almost one-half (47%) of chlamydia-tested and two-thirds (66%) of chlamydia+gonorrhoea-tested women reported symptoms.

Table 1 Prevalence of PID by patient characteristics for chlamydia-tested and chlamydia+gonorrhoea-tested women

	Chlamydia-tested (N=15 690) PID/patients		Chlamydia +gonorrhoea-tested* (N=8839) PID/patients	
	n/N	Per cent	n/N	Per cent
	436/15 690	2.8	419/8839	4.7
Age group (years)				
16–29	359/12 080	3.0	345/6596	5.2
30–49	77/3610	2.1	74/2243	3.3
Country of birth				
Australia	188/6529	2.9	182/3591	5.1
Other	248/9161	2.7	237/5248	4.5
Current contraception				
Any hormonal	119/4362	2.7	114/2185	5.2
IUD	18/263	6.8	17/157	10.8
Other/not reported	299/11 065	2.7	288/6497	4.4
Symptoms self-reported at triage				
No	49/8348	0.6	46/3005	1.5
Yes	387/7342	5.3	373/5834	6.4
STI contact				
No	397/14 652	2.7	383/8322	4.6
Yes	39/1038	3.8	36/517	7.0
Chlamydia test results				
Negative	342/14 411	2.4	NA	
Positive	94/1279	7.4	NA	
Chlamydia and gonorrhoea test results				
Negative	NA		327/8106	4.0
Chlamydia positive only	NA		82/681	12.0
Gonorrhoea positive only	NA		5/30	16.7
Chlamydia and gonorrhoea positive	NA		5/22	22.7
Male sexual partners, last 3 months				
None	10/1239	0.8	10/660	1.5
1	231/8059	2.9	225/4628	4.8
≥2	195/6392	3.1	187/3551	5.3
Condom use with male partners, last 3 months				
No male partners/vaginal sex	11/1351	0.8	11/715	1.5
Always	44/2572	1.7	44/1267	3.5
Not always	381/11 767	3.2	364/6857	5.3
Male sexual partners, last 12 months				
None	3/514	0.6	3/273	1.1
1	117/4059	2.9	113/2457	4.6
2	90/3418	2.6	86/1873	4.6
≥3	226/7699	2.9	217/4236	5.1
Condom use with male partners, last 12 months				
No male partners/vaginal sex	5/612	0.8	5/323	1.6
Always	38/2299	1.7	38/1149	3.3
Not always	393/12 779	3.1	376/7367	5.1

*Chlamydia+gonorrhoea tested group is a subset of the chlamydia-tested group.
IUD, intrauterine device; NA, not applicable; PID, pelvic inflammatory disease; STI, sexually transmitted infection.

Individual factors associated with increased risk of a PID diagnosis

Among chlamydia-tested women, multivariable analysis found PID diagnosis was more likely (table 2) with chlamydia infection (adjusted odds ratio (AOR) 3.0, 95% CI 2.4 to 3.9), an IUD (AOR 2.6, 95% CI 1.6 to 4.2) and younger age (AOR 1.3, 95% CI 1.0 to 1.6) and less likely with consistent condom use (AOR 0.6, 95% CI 0.4 to 0.8).

Among the chlamydia+gonorrhoea-tested subset, PID diagnosis was more likely (table 2) with chlamydia infection only (AOR 3.0, 95% CI 2.3 to 3.9), gonorrhoea only (AOR 4.4, 95% CI 1.7 to 11.6), chlamydia+gonorrhoea co-infection (AOR 6.2, 95% CI 2.2 to 17.0), an IUD (AOR 2.6, 95% CI 1.5 to 4.4) and younger age (AOR 1.4, 95% CI 1.1 to 1.9).

Population attributable fraction

The adjusted PAF for PID (table 3) for chlamydia was 14.1% (95% CI% 9.9 to 18.0%) for chlamydia-tested women. For chlamydia+gonorrhoea-tested women, the PAF was higher for chlamydia only (12.4%, 95% CI 8.4% to 16.2%) than gonorrhoea only (0.9%, 95% CI −0.1% to 1.8%) or chlamydia+gonorrhoea co-infection (1.0%, 95% CI 0.0% to 1.9%) (table 3). Stratified by age group, the adjusted chlamydia PAF among chlamydia-tested women was 14.5% (95% CI 9.8% to 19.1%) for women aged 16–29 years and 11.7% (95% CI 3.2% to 19.4%) for those aged 30–49 years. Stratified by symptoms at triage, the chlamydia PAF for women not reporting symptoms was 27.8% (95% CI 11.6% to 41.0%) and for women reporting symptoms it was 13.2% (95% CI 9.1% to 17.1%).

Sensitivity analysis

Online supplementary table S1 presents the demographic characteristics and PID prevalence among the 18 586 eligible women and two analytical subgroups. The proportion 16–29 years and Australian born was similar between all groups. Online supplementary table S2 presents the estimated AORs

Table 2 Factors associated with PID among chlamydia-tested and chlamydia+gonorrhoea-tested women

	Chlamydia-tested (N=15 690)					Chlamydia+gonorrhoea-tested* (N=8839)				
	Univariable		Multivariable			Univariable		Multivariable		
	OR	95% CI	AOR	95% CI	p Value	OR	95% CI	AOR	95% CI	p Value
Age group (years)										
16–29	1.4	1.1 to 1.8	1.3	1.0 to 1.6	0.058	1.6	1.3 to 2.1	1.4	1.1 to 1.9	0.006
30–49	1.0		1.0			1.0		1.0		
Country of birth										
Australia	1.1	0.9 to 1.3				1.1	0.9 to 1.4			
Other	1.0					1.0				
Current contraception										
Any hormonal	1.0	0.8 to 1.3	0.9	0.7 to 1.1	0.210	1.2	0.9 to 1.5	1.0	0.8 to 1.3	0.789
IUD	2.6	1.6 to 4.3	2.6	1.6 to 4.2	<0.001	2.6	1.6 to 4.4	2.6	1.5 to 4.4	<0.001
Other/not reported	1.0		1.0			1.0		1.0		
Chlamydia test results										
Negative	1.0		1.0			NA				
Positive	3.3	2.6 to 4.1	3.0	2.4 to 3.9	<0.001	NA				
Chlamydia and gonorrhoea test results										
Negative	NA					1.0		1.0		
Chlamydia positive only	NA					3.3	2.5 to 4.2	3.0	2.3 to 3.9	<0.001
Gonorrhoea positive only	NA					4.8	1.8 to 12.5	4.4	1.7 to 11.6	0.003
Chlamydia and gonorrhoea positive	NA					7.0	2.6 to 19.1	6.2	2.2 to 17.0	<0.001
Male sexual partners, last 3 months†										
None	1.0					1.0				
1	3.6	1.9 to 6.8				3.3	1.7 to 6.2			
≥2	3.9	2.0 to 7.3				3.6	1.9 to 6.9			
Condom use with male partners, last 3 months										
No male partners/vaginal sex	0.2	0.1 to 0.4	0.3	0.1 to 0.5	<0.001	0.3	0.2 to 0.5	0.3	0.2 to 0.6	<0.001
Always	0.5	0.4 to 0.7	0.6	0.4 to 0.8	<0.001	0.6	0.5 to 0.9	0.7	0.5 to 1.0	0.026
Not always	1.0		1.0			1.0		1.0		
Male sexual partners, last 12 months†										
None	1.0					1.0				
1	5.1	1.6 to 16.0				4.3	1.4 to 13.7			
2	4.6	1.5 to 14.6				4.3	1.4 to 13.8			
≥3	5.2	1.6 to 16.1				4.9	1.5 to 15.3			
Condom use with male partners, last 12 months†										
No male partners/vaginal sex	0.3	0.1 to 0.6				0.3	0.1 to 0.7			
Always	0.5	0.4 to 0.7				0.6	0.5 to 0.9			
Not always	1.0					1.0				

*Chlamydia+gonorrhoea-tested group is a subset of the chlamydia-tested group.
†Male sexual partners, last 3 and 12 months, and condom use, last 12 months, omitted from final multivariable models due to collinearity.
NA, not applicable; PID, pelvic inflammatory disease.

Table 3 PAF of PID associated with chlamydia and gonorrhoea infection

	Overall		No symptoms at triage*		Symptoms at triage†	
	PAF % (95% CI)	Adjusted PAF‡ % (95% CI)	PAF % (95% CI)	Adjusted PAF‡ % (95% CI)	PAF % (95% CI)	Adjusted PAF‡ % (95% CI)
Chlamydia-tested						
Chlamydia positive	14.6 (10.4 to 18.6)	14.1 (9.9 to 18.0)	28.3 (12.2 to 41.4)	27.8 (11.6 to 41.0)	13.6 (9.5 to 17.5)	13.2 (9.1 to 17.1)
Chlamydia+ gonorrhoea-tested subset						
Chlamydia and/or gonorrhoea positive	14.9 (10.7 to 18.9)	14.2 (10.0 to 18.3)	25.5 (0.9 to 38.8)	24.4 (8.0 to 37.9)	14.1 (9.9 to 18.1)	13.6 (9.4 to 17.6)
Chlamydia positive only	13.0 (9.0 to 16.8)	12.4 (8.4 to 16.2)	19.6 (4.8 to 32.0)	18.5 (3.5 to 31.2)	12.6 (8.6 to 16.5)	12.2 (8.2 to 16.1)
Gonorrhoea positive only	0.9 (−0.1 to 1.9)	0.9 (−0.1 to 1.8)	1.9 (−2.3 to 5.8)	1.8 (−2.3 to 5.8)	0.8 (−0.1 to 1.7)	0.8 (0.1 to 1.7)
Chlamydia and gonorrhoea positive	1.0 (0.1 to 1.9)	1.0 (0.0 to 1.9)	4.1 (−1.4 to 9.3)	4.1 (−1.3 to 9.2)	0.6 (−0.2 to 1.4)	0.6 (−0.2 to 1.4)

*Chlamydia infection was detected in 746 (8.9%, 95% CI 8.3% to 9.6%) and PID was diagnosed in 49 (0.6%, 95% CI 0.4% to 0.8%) of 8348 chlamydia-tested women not reporting symptoms at triage.
†Chlamydia infection was detected in 533 (7.3%, 95% CI 6.7% to 7.9%) and PID was diagnosed in 387 (5.3% 95% CI 4.8% to 5.8%) of 7342 chlamydia-tested women reporting symptoms at triage.
‡Adjusted for age group, contraception, condom use, last 3 months.
PAF, population attributable fraction; PID, pelvic inflammatory disease.

from multiple imputation. The estimated AORs for PID from chlamydia-tested, chlamydia+gonorrhoea-tested and multiple imputation complete-case analyses were very similar. For example, the chlamydia AOR was 3.2 (95% CI 2.5 to 4.0) in the first imputation model with missing chlamydia test result values imputed compared with 3.0 (95% CI 2.3 to 4.9) in chlamydia-tested women.

DISCUSSION

This study found that in high-risk female SHC patients, up to 14% of clinically diagnosed PID was associated with a current chlamydia infection and about 1% with gonorrhoea. Among women not reporting symptoms at triage, the chlamydia PAF was 28% compared with 13% for women reporting symptoms. It is likely the lower PAF in symptomatic women is because factors other than chlamydia (such as symptoms, another STI) influenced PID diagnosis whereas for asymptomatic women, chlamydia detection facilitated PID diagnosis. At the individual level, our multivariable analysis showed PID diagnosis was more likely with chlamydia or gonorrhoea infection, an IUD, inconsistent condom use and in younger women.

This is the first Australian study, and we believe internationally, to estimate the PAF of PID associated with chlamydia or gonorrhoea using clinical data. PAF represents the proportion of disease in a population that might be avoided if particular risk factors were eliminated.[15] At the individual level, we found a 4.4-fold and 3-fold increased risk of PID for women with gonorrhoea or chlamydia, respectively. This is consistent with a recent Australian study showing higher PID hospitalisation rates following gonorrhoea or chlamydia compared with no infection.[19] Despite a strong individual association between gonorrhoea and PID, our gonorrhoea PAF was small reflecting its low prevalence (<0.5%) in this population and consistent with the pattern of largely male-to-male gonorrhoea transmission in Australia.[5] Chlamydia was more prevalent in our population, and this is reflected in our PAF estimates with a larger burden of PID in this population potentially avoidable by eliminating a chlamydia rather than a gonorrhoea infection.

The burden of PID related to STIs at population level will vary between populations depending on the underlying prevalence of STIs and other risk factors. Our PAF estimates are based in a high-risk SHC population and may not reflect the general population. Around half our study population reported symptoms at triage and three or more MSPs in the past year. This is higher than observed among women attending Australian general practices where 6% are symptomatic and 13% report three or more MSPs in a year.[20] The chlamydia prevalence in our sample (7.3% in symptomatic, 8.9% in asymptomatic women) was also higher compared with 4.4% in Australian general practice.[20] Although our PAF estimates suggest that removing chlamydia might reduce the PID burden by 14% (95% CI 10% to 18%), most PID in this high-risk population was not associated with chlamydia. Elsewhere, modelling has estimated that around 20% (5% –40%) of PID among UK women is caused by chlamydia.[21] Of concern is our finding that around two-thirds of chlamydia-associated PID was co-diagnosed at first visit, suggesting symptoms rather than awareness of STI risk prompted the visit. Reduction in chlamydia-associated PID morbidity is possible only if women present early in their infection's course, highlighting the ongoing need for improving community awareness around STI risk, indications for testing and ensuring testing is accessible.

PID prevention is widely viewed as a potential measure of the impact of chlamydia screening or opportunistic testing. Such programs could prevent PID indirectly if they lead to decreased chlamydia prevalence, or directly if chlamydia is detected and treated before PID develops.[22] Success of direct prevention depends on the duration between chlamydia acquisition and PID development, which can be weeks.[11 23] Some countries have conducted chlamydia screening or opportunistic testing trials focussing on young asymptomatic adults in community settings and included PID as an outcome measure[9 14 24 25] Results from a UK trial (PID incidence in chlamydia-screened (1.3%) vs unscreened (1.9%)) suggested chlamydia screening might reduce PID incidence over 1 year[9] while a Dutch trial reported a low 1 year PID incidence (1.9%) that did not alter over time.[24] Furthermore, a Swedish population-based cohort found a low cumulative PID incidence (to age 35) (5.6% in women ever chlamydia positive vs 4% in chlamydia negative)[26] and concluded the benefits of chlamydia screening may have been overestimated.

So, what do our results mean for opportunistic chlamydia screening in general-practice settings? Our subanalysis showed that chlamydia elimination for high-risk symptomatic female

SHC attendees with a PID prevalence of 5.3% (53 cases per 1000 patients) might avoid 13% of PID, or 6.9 cases per 1000 patients. Given women attending Australian general practice are more likely to be asymptomatic[20] and if we assume the general-practice PID prevalence is comparable with that observed among women not reporting symptoms in this study (0.6%), then with a PAF of 28%, chlamydia elimination might only avoid 1.7 cases per 1000 patients. However, this is most likely overestimated because chlamydia prevalence in general practice (4.4% in women)[20] is considerably lower than we observed for women not reporting symptoms (8.9%). Furthermore, it is only PID cases diagnosed after chlamydia detection and treatment that could be directly prevented by screening.

Our analysis is strengthened by the large sample size and sensitivity analysis showing missing data did not impact on the association with PID. Another strength is our adjusted PAF estimates accounted for the effects of potentially confounding variables on the relationship between chlamydia or gonorrhoea and PID.

This study has a number of limitations. The cross-sectional design means the temporal relationship between STIs and most PID is unknown and not all women were chlamydia and gonorrhoea tested, potentially biasing PAF estimates to higher-risk women. Our decision to undertake a cross-sectional analysis was influenced by the clinical setting; female non-sex-workers are only triaged into MSHC if at STI risk and repeat visits limited to the next 2–4 weeks. Restricting our study to first episode of care maximised data completeness. Second, PID diagnosis was clinical, which can vary in accuracy between clinicians.[27] If clinicians were oversensitive to PID when STIs were diagnosed, the PAF could be overestimated. Third, although past or repeated chlamydia infection are both PID risk factors,[28] we were unable to measure their contribution; possibly the PAF would be higher if previous infection was considered.

We found that an IUD in situ was associated with increased PID risk. The role of IUDs in PID has been debated with higher PID rates reported in IUD users than in non-users. This risk appears greatest in the 3 months post insertion,[1] relevant to copper/levonorgestrel-releasing IUDs and for women with an STI during insertion.[29] However, a recent review found no evidence that IUD use increases PID risk in excess of risk from an STI.[29] Observational studies may be hampered by detection bias. It is possible that clinicians in this study had a lower threshold for PID diagnosis when they knew a woman had an IUD.

Interestingly, we found no pathogen in 61% PID cases. Almost a quarter had chlamydia and/or gonorrhoea which is similar to UK sex-workers with clinically diagnosed PID,[28] but lower than past US and European studies (1970s–1990s) where chlamydia was cultured from 5% to 51% and gonorrhoea from 5% to 80% PID cases.[1] MG and BV were detected in some PID cases in this study suggesting an aetiological role, although evidence has established one for MG[2] but not BV[3] The fact that no infection was diagnosed for over half our PID cases raises questions about sensitivity and specificity of PID clinical diagnosis and highlights the need for a gold standard diagnostic test. Several groups are investigating PID diagnostic biomarkers, but are some way off.[30] It is also possible for some PID cases with no pathogen detected that a pathogen had cleared from the lower genital tract but had ascended to the upper genital tract.

Justification of chlamydia (and gonorrhoea) screening often includes prevention of female reproductive morbidity. PAF provides a measure of PID burden that might be avoided by preventing these STIs. In this high chlamydia prevalence population, most PID diagnoses were not associated with chlamydia and chlamydia elimination might at most reduce PID by 14%. Our results suggest that in a general-practice setting with low chlamydia prevalence, widespread chlamydia screening would only prevent a small number of PID cases raising questions about the cost-effectiveness of chlamydia screening. Nevertheless, improved community awareness around STI risk and indications for testing is essential to reach high-risk women, to diagnose and treat infections promptly and avoid progression to PID.

Key messages

- Population attributable fraction (PAF) can provide a measure of pelvic inflammatory disease (PID) burden in a population that might be eliminated by preventing chlamydia or gonorrhoea infection.
- Most PID in women attending an Australian sexual-health-clinic was not associated with chlamydia. Chlamydia elimination in this high chlamydia prevalence population might only reduce PID by 14%.
- In general-practice settings with low chlamydia prevalence, chlamydia elimination could only prevent a small number of PID cases.
- Reduction in sexually transmitted infection (STI)-associated PID morbidity is possible only if women present early in their infection. Improved community awareness around STI risk and indications for testing is essential.

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3.2 Chapter summary

This publication reported on 18,586 new female patients to an Australian sexual health clinic; among whom 15,690 were tested for chlamydia, 8.2% tested chlamydia positive, 2.8% were diagnosed with PID and the aPAF for chlamydia was 14.1%. Among a subset (n=8,839) of women 0.3% were gonorrhoea positive only, 0.2% were gonorrhoea and chlamydia positive, 4.7% were diagnosed with PID, and the aPAF for gonorrhoea was 1%.

This new information based on the PAF suggests that for a high chlamydia prevalence clinic population, eliminating chlamydia might at most reduce PID by 14% and eliminating gonorrhoea might only avoid 1% of PID. A sub-group analysis assessed the PAF of chlamydia for PID in asymptomatic women, in recognition that asymptomatic presentation might be more common for women attending general practice, being the setting where most chlamydia screening would occur if implemented in Australia. The findings suggested that in a setting with low chlamydia prevalence, chlamydia elimination might only prevent a small number of PID cases. The chlamydia PAF for PID (14%) reported in this publication is lower than the estimate of 19.7% reported for women aged 16 to 44 years in recent modelling for the contribution of chlamydia to PID (see Section 2.2.1). The modelled estimates were adjusted for under-ascertainment of chlamydia in PID cases that can bias retrospective studies.[109] A limitation of the PAF analysis in this thesis was that the association of chlamydia to sub-clinical PID could not be included in PAF estimates.

The publication reported a 4.4-fold higher odds of a PID diagnosis for women with gonorrhoea and a 3-fold higher odds for women with a chlamydia infection. In view of this high individual risk of PID associated with gonorrhoea, an increased risk of PID hospitalisation after gonorrhoea,[40 41] and, recent increases in gonorrhoea rates for Australian women,[34] a continued focus on gonorrhoea and chlamydia case detection and PID diagnosis for women at STI risk or presenting with pelvic pain is essential. Case detection must be complemented by other aspects of management including timely partner management and retesting after treatment toward reducing reinfections and PID.

This manuscript was selected as editor's choice on the journal website.

Chapter 4: Characteristics of pathogen negative PID

PUBLISHED: Goller JL, De Livera AM, Fairley CK, Guy RJ, Bradshaw CS, Chen MY, Hocking JS. Characteristics of pelvic inflammatory disease where no sexually transmitted infection is identified: a cross-sectional analysis of routinely collected sexual health clinic data. *Sexually Transmitted Infections,* 2017 93(1):68-70. doi:10.1136/sextrans-2016-052553

4.1 Introduction

An additional finding in Chapter 3, was that 61% of PID cases did not have an infection identified. The clinical features of PID are known to vary with different pathogens; recent onset abdominal pain has been reported more often by women with gonorrhoeal PID than chlamydial PID[85] and systemic inflammatory markers are more common in women with gonorrhoeal PID than chlamydial or *M. genitalium* PID.[140] However, the characteristics of PID without an identified pathogen have been infrequently reported.

Chapter 4 presents findings from a further analysis of routinely collected sexual health clinic data that was published in *Sexually Transmitted Infections.*[269] The study population comprised 330 women with clinically diagnosed PID and all were tested for chlamydia, gonorrhoea, *M. genitalium* and bacterial vaginosis. The demographic, behavioural and clinical characteristics of pathogen-negative PID (a PID diagnosis where chlamydia, gonorrhoea, *M. genitalium* and bacterial vaginosis tests conducted during the visit were all negative) were compared with pathogen-positive PID (a PID diagnosis and positive test for one or more of chlamydia, gonorrhoea, *M. genitalium* or bacterial vaginosis). The methods in this chapter are detailed in the following publication. Due to the analysis being based on available data from the electronic patient record the clinical variables consisted of laboratory test results and assessment of vaginal inflammation measured by poly-morphonuclear leucocyte count from high vaginal swab specimens. Multivariable logistic regression was conducted to assess whether pathogen-negative PID differed to pathogen-positive PID, with the analysis clustered by doctor to account for any variability in PID diagnosis between clinicians.

SHORT REPORT

Characteristics of pelvic inflammatory disease where no sexually transmitted infection is identified: a cross-sectional analysis of routinely collected sexual health clinic data

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ABSTRACT

Objectives Pelvic inflammatory disease (PID) occurs when pathogens, often sexually transmitted, ascend to the upper genital tract, yet a causative pathogen is not detected in a substantial proportion of diagnosed PID. We assessed the characteristics associated with PID in women in whom chlamydia, gonorrhoea, *Mycoplasma genitalium* (MG) and bacterial vaginosis (BV) were not detected ('pathogen-negative-PID').

Methods Cross-sectional analysis of routinely collected clinical data from new female patients attending a sexual health clinic between 2006 and 2013. Women were eligible if they had been diagnosed with PID and tested for genital chlamydia, gonorrhoea, MG and BV. Logistic regression was conducted to identify characteristics associated with pathogen-negative-PID.

Results Among 330 women with clinically diagnosed PID, 204 (61.8%, 95% CI 56.3% to 67.1%) had pathogen-negative-PID. Compared with pathogen-positive-PID, pathogen-negative-PID cases were more likely to be aged ≥30 years (adjusted odds ratio (AOR) 1.7, 95% CI 1.0 to 3.0), had less evidence of vaginal inflammation (AOR 0.5, 95% CI 0.3 to 0.9) and reported less unprotected sex (AOR 0.6, 95% CI 0.4 to 1.0).

Conclusions These findings highlight uncertainties around PID diagnosis and aetiology. Pathogen-negative-PID could represent (i) a false positive diagnosis where the woman does not have a sexually transmitted infection (STI) or PID, (ii) PID of another microbiological aetiology or associated with a past STI or (iii) PID where the cervical infection has cleared. However, until diagnostic biomarkers are available, PID treatment should be based on clinical features and sexual risk.

BACKGROUND

Pelvic inflammatory disease (PID) is a clinical syndrome involving female upper genital tract (UGT) inflammation following pathogen ascent from the lower genital tract. The sexually transmitted infections (STIs), *Chlamydia trachomatis* (chlamydia) and *Neisseria gonorrhoeae* (gonorrhoea) are well-known causes of PID[1] with an aetiological role established for *Mycoplasma genitalium* (MG).[2] A range of bacteria, many endogenous to the vaginal microbiota or occurring in increased concentrations with bacterial vaginosis (BV) have been isolated from the UGT of women with PID.[1]

Despite this array of microbial species, recent studies in high-income countries have not detected a causative pathogen in a substantial proportion of PID. In the USA, 17% of emergency department PID had chlamydia and/or gonorrhoea[3] and 23% of PID in an inpatient/outpatient treatment trial had chlamydia, gonorrhoea and/or MG.[4] In the UK, a case–control study found no aetiological agent in 64% PID.[5] Although PID features vary by microbial cause[1 4] its characteristics without an identified infectious pathogen have been infrequently reported. In a recent analysis of Australian sexual health clinic (SHC) data examining the association between chlamydia or gonorrhoea and PID we detected neither infection in over half of PID cases,[6] prompting questions whether the characteristics of PID without an identified pathogen differed to PID with a pathogen and if this information might enhance patient triage. In this study, we sought to assess the characteristics associated with PID in women where no concurrent STI or BV was detected.

METHODS

We conducted a cross-sectional study using retrospective routinely collected SHC data. New female, non-sex worker patients between January 2006 and June 2013, aged 16–49 years, diagnosed with PID and tested for chlamydia, gonorrhoea, MG and BV were eligible. The study population here which consisted of 204 (pathogen-negative-PID) cases and 126 (pathogen-positive-PID) controls would allow us to detect an OR of 2 at a significance level of 5% with 85% power, assuming that 50% of (pathogen-positive-PID) controls were exposed to the risk factor of interest.

Melbourne Sexual Health Centre is the major public SHC in the Australian state of Victoria. Attendees assessed at high sexual risk via their sexual history, self-reported risk behaviours, symptoms suggesting an STI, STI contacts or women with pelvic pain are triaged in. Chlamydia testing is offered to new female patients. Specific signs/symptoms guide testing women for other STIs: gonorrhoea for symptomatic women with vaginal discharge, cervicitis or suspected PID; MG for mucopurulent cervicitis, MG contacts or suspected PID; BV for vaginal discharge or suspected PID and trichomonas for symptomatic, high-risk women. High vaginal swabs (HVSs) for microscopy

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are indicated by vaginal discharge, odour, pain or intermenstrual bleeding.

The primary study outcome was 'pathogen-negative-PID' (a PID diagnosis where chlamydia, gonorrhoea, MG and BV tests conducted during the visit were negative). Pathogen-negative-PID cases were compared with pathogen-positive-PID (PID and testing positive for at least one of chlamydia, gonorrhoea, MG, BV). Clinical PID diagnosis was guided by minimum criteria of uterine, cervical motion or adnexal tenderness in sexually active women with pelvic pain.[7] STI diagnoses were laboratory confirmed: chlamydia by strand displacement amplification from urine, HVS and cervical swabs; gonorrhoea by microscopy of Gram-stained cervical swab and culture; MG by polymerase chain reaction on urine, HVS or cervical swab and BV by microscopy, predominantly a Nugent score of 7–10 or 4–6 with clue cells. Presence of vaginal inflammation was assessed by HVS polymorphonuclear leucocyte (PMNL) count and defined as ≥5 PMNL per 1000 high-powered field.

Demographic, sexual behaviour (condom use, number of male sexual partners (MSPs)), clinical information (intrauterine device (IUD) in situ, PMNL, chlamydia, gonorrhoea, MG, BV results) were extracted from the electronic record. Records with incomplete sexual behaviour (n=9) or no PMNL (n=1) were excluded. Trichomonas results were extracted where available.

The Alfred Health Human Research Ethics Committee (EC00315) provided study approval.

Statistical analysis

Age, number of MSP, unprotected sex with non-regular MSP, IUD in situ and presenting as an STI contact were identified a priori as potential confounders. Univariable and multivariable logistic regression was conducted to identify characteristics associated with pathogen-negative-PID. As clinical PID diagnosis can vary by clinician[8] we accounted for clustering within clinician by obtaining robust variance estimates that adjust for within-cluster correlation.[9] Results are reported as OR with 95% CIs. Analyses were conducted using STATA V.13.0.

RESULTS

During the study period, PID was diagnosed in a total of 330 new patients who were tested for chlamydia, gonorrhoea, MG and BV; 312(95%) had trichomonas tests. Of these 330 women, 204 (61.8%; 95% CI 56.3% to 67.1%) had pathogen-negative-PID and 126 had pathogen-positive-PID (49.2% (95% CI 40.4% to 58.1%) had chlamydia, 6.3% (95% CI 2.0% to 10.7%) had gonorrhoea, 11.9% (95% CI 6.2% to 17.6%) had MG and 56.3% (95% CI 47.6% to 65.1%) had BV). Two women tested trichomonas positive (one each from the pathogen-negative and pathogen-positive-PID groups).

Compared with pathogen-positive PID, women with pathogen-negative PID (table 1) were more likely to be aged ≥30 years (AOR 1.7, 95% CI 1.0 to 3.0) and less likely to have

Table 1 Characteristics of the study population and associations for pathogen-negative PID

	Pathogen-positive-PID (n=126) n (%)	Pathogen-negative-PID (n=204) n (%)	Univariable OR (95% CI)	Multivariable AOR (95% CI)
Age group in years				
16–29	111 (88.1)	165 (80.9)	1.0	1.0
30–49	15 (11.9)	39 (19.1)	1.7 (1.0 to 3.1)	1.7 (1.0 to 3.0)*
Born in Australia				
No	76 (60.3)	111 (54.4)	1.0	
Yes	50 (39.7)	93 (45.6)	1.3 (0.8 to 2.1)	
STI contact‡				
No	112 (88.9)	193 (94.6)	1.0	1.0
Yes	14 (11.1)	11 (5.4)	0.5 (0.2 to 1.1)	0.4 (0.2 to 1.1)
IUD in situ				
No	120 (95.2)	197 (96.6)	1.0	1.0
Yes	6 (4.8)	7 (3.4)	0.7 (0.2 to 2.0)	0.7 (0.3 to 2.0)
More than one MSP, last 3 months†				
No	61 (48.4)	120 (58.8)	1.0	
Yes	65 (51.6)	84 (41.2)	0.7 (0.4 to 1.0)	
Unprotected sex with non-regular MSP, last 3 months				
No	64 (50.8)	127 (62.3)	1.0	1.0
Yes	62 (49.2)	77 (37.8)	0.6 (0.4 to 1.0)	0.6 (0.4 to 1.0)*
More than one MSP, last 12 months†				
No	27 (21.4)	55 (27.0)	1.0	
Yes	99 (78.6)	149 (73.0)	0.7 (0.4 to 1.4)	
Unprotected sex with non-regular MSP, last 12 months†				
No	34 (27.0)	67 (32.8)	1.0	
Yes	92 (73.0)	137 (67.2)	0.8 (0.4 to 1.5)	
Vaginal inflammation present§				
No	65 (51.6)	135 (66.2)	1.0	1.0
Yes	61 (48.4)	69 (33.8)	0.5 (0.3 to 0.9)	0.5 (0.3 to 0.9)¶

*p≤0.05.
†The variables, more than one MSP (last 3 and 12 months), and unprotected sex with non-regular MSP (last 12 months) omitted from final multivariable models due to collinearity.‡STI contact provided as a reason for attending the clinic.
§Presence of vaginal inflammation defined as ≥5 polymorphonuclear leucocytes per 1000 high-powered field on high vaginal swab.
¶p≤0.01. IUD, intrauterine device; MSP, male sexual partner; PID, pelvic inflammatory disease; STI, sexually transmitted infection.

vaginal inflammation (AOR 0.5, 95% CI 0.3 to 0.9) or report recent unprotected sex (AOR 0.6, 95% CI 0.4 to 1.0).

DISCUSSION

This study found no aetiological agent in 62% of women with clinically diagnosed PID. Similar levels of PID without an identified pathogen have been reported.[3–5] Women in this study, with clinical evidence of PID but no pathogen were older, less likely to have vaginal inflammation, or report recent unprotected sex than women with chlamydia, gonorrhoea, MG and/or BV-associated PID. We also found no difference between pathogen-negative and pathogen-positive-PID regarding an IUD in situ or presenting as STI contacts.

The high proportion of pathogen-negative-PID here raises two key questions. First, are these cases PID or are they false positive diagnoses? It is well known that clinical PID diagnosis is imprecise, which is our study's main limitation. There is no specific non-invasive diagnostic test or physical feature both sensitive and specific to PID diagnosis[1] which can also vary by clinician and experience.[8] Pelvic pain is a key PID characteristic but its duration, intensity and cause can vary. Clinicians must consider whether the sexual history, symptoms and signs suggest PID or another diagnosis. Laparoscopy is often considered the diagnostic gold standard but is invasive and impractical for most outpatient settings and can miss early infection.[1] Minimum clinical diagnostic criteria of uterine, cervical motion or adnexal tenderness in sexually active women with recent onset pelvic pain is the mainstay of PID diagnosis and initiating mild–moderate PID treatment internationally.[7] Local guidelines in this SHC are based on these minimum criteria[7] and aim to promote a low threshold for prescribing PID pharmacotherapy, minimise PID cases that are missed and prevent future reproductive morbidity. This may result in overtreatment, but it has been argued PID overdiagnosis is better than underdiagnosis (providing other diagnoses are excluded) as the risks of antibiotics are potentially less than from possible sequelae associated with ongoing untreated infection.[1 7] Although we found a lower sexual risk in pathogen-negative-PID, the overall study population was high risk; representing <2% of new female patients during the study and over half (52%) reporting three or more MSP in a year compared with 3.4% women surveyed nationally.[10] In this high-risk population, clinicians may have been sensitive to PID risk and consequently overcautious when diagnosing PID, although overdiagnosis may have varied by clinician experience.[8]

Second, are these PID cases caused by an unidentified pathogen or past infection? Respiratory, enteric[1] or novel bacteria[11] have occasionally been isolated in non-gonococcal/non-chlamydial PID as have chlamydia or MG from the UGT of salpingitis cases without cervical infection.[12] Further, a past STI has been associated with increased PID risk.[5] Although guidelines chiefly recommend testing suspected PID cases for chlamydia and gonorrhoea[7] there is a need to understand via clinical or genetic microbiome studies[11] the potential for other known or novel pathogens to ascend to the UGT and cause symptoms.

The main characteristic differentiating women with pathogen-negative and pathogen-positive-PID was reduced evidence of vaginal inflammation. Other studies have assessed purulent vaginal/cervical discharge as PID diagnostic tests, but, with mixed results their use in improving diagnostic certainty has not been shown.[13] Uncertainty around clinical PID diagnosis highlights the need for objective diagnostic methods, with development of sensitive and specific non-invasive biomarkers for female-UGT infection a research priority.[1] Promisingly, different ribonucleic acid biosignatures (many involved in inflammation) were recently identified in peripheral blood of a small sample of PID cases.[14]

This study's key strength is that pathogen-negative and pathogen-positive-PID cases are from the same SHC, limiting variability in practice between patient group for STI/BV and PID diagnoses. The analysis is further strengthened by accounting for correlation in clinical practice within clinicians.

These findings highlight an area of considerable uncertainty around PID diagnosis and aetiology. Pathogen-negative-PID could be because: (i) these women do not have an STI or PID; (ii) an STI had cleared from the cervix but had ascended to the UGT causing PID or (iii) it is PID caused by an unidentified pathogen or past STI. Until we have well-validated rapid biomarkers that improve precision of clinical PID diagnosis, it would be prudent to maintain the basis for PID diagnosis and treatment on clinical features and sexual risk rather than microbiological findings.

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Contributors JLG collected the data, conducted the analysis and wrote the manuscript. AMDL supervised the analysis and contributed to the manuscript. JH, RG, CKF, CB and MYC contributed to the design and/or interpretation, provided feedback and contributed to the manuscript. All authors approved the final submitted version of the manuscript.

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4.2 Chapter summary

The publication in Chapter 4 identified that of 330 women with clinically diagnosed PID, that 62% had no pathogen identified. This finding is consistent with other studies finding no pathogen in a large proportion of PID cases.[18 19 140] Women in this study with clinical evidence of PID but no pathogen were more likely to be aged ≥30 years (AOR 1.7, 95%CI 1.0, 3.0) and less likely to have evidence of vaginal inflammation (AOR 0.5, 95%CI 0.3, 0.9) or to report recent unprotected sex (AOR 0.6, 95%CI 0.4, 1.0) than women with chlamydia, gonorrhoea, *M. genitalium* and/or bacterial vaginosis associated PID.

The findings illustrate uncertainties about PID diagnosis and aetiology and the need for biomarkers of upper genital tract inflammation that can improve certainty of a PID diagnosis. In the absence of well validated, objective and non-invasive diagnostic methods for PID diagnosis, the decision to initiate treatment for mild to moderate PID is reliant on sensitive minimum clinical criteria that aim to lessen the number of PID cases that are missed.[13] The publication highlights the need for clinicians to weigh up the potential consequences of under-diagnosis of PID that could result in future adverse reproductive impacts[270] versus over-diagnosis of PID that exposes women to unneeded antibiotic treatment. However, reported side effects requiring discontinuation of PID treatment are infrequent.[213] Although the study found that pathogen negative PID cases were at lower sexual risk than pathogen positive PID, the overall study population was high risk when compared to a national sample.[271] Sexual risk is an important factor for clinicians when considering differential diagnoses for a woman with new onset low abdominal pain.

The main characteristic differentiating women with pathogen-negative and pathogen-positive-PID was reduced evidence of vaginal inflammation. Several studies have assessed indicators of lower genital tract inflammation for their use in supporting a PID diagnosis, but providing mixed evidences. The presence of mucopus or white blood cells in vaginal discharge from a sample of women enrolled in the PEACH study was shown to be a sensitive test for upper genital tract infection (as confirmed by endometrial biopsy).[203] In contrast, a review of 13 studies (including the PEACH study) reported that for women with clinical evidence of PID that the presence or absence of vaginal or cervical discharge was not helpful in making or excluding a PID diagnosis.[272]

Chapter 4 also provides updated evidence about the frequency of pathogens in Australian PID cases that can inform PID management guidelines. Among the 330 PID cases in this publication, bacterial vaginosis was the most frequent infection, diagnosed in 21.5% (n=71) cases, followed by chlamydia (18.8%, n=62), *M. genitalium* (4.5%, n=15) and gonorrhoea (2.4%, n=8). In addition to the published results, 25 of the PID cases had more than one infection diagnosed, all but two were coinfected with bacterial vaginosis. The breakdown of these coinfections included chlamydia and bacterial vaginosis (n=13), *M. genitalium* and bacterial vaginosis (n=4), chlamydia, gonorrhoea and bacterial vaginosis (n=4), chlamydia and *M. genitalium* (n=2), and one each of gonorrhoea and bacterial vaginosis, and, chlamydia, *M. genitalium* and bacterial vaginosis.

The microbial causes of PID are difficult to determine. Respiratory, enteric or novel bacteria and bacterial vaginosis associated pathogens have been identified in the upper genital tract of women with non-gonococcal or non-chlamydial PID, although some of these pathogens have also been present in women without PID.[2 96-99] PID is associated with bacterial vaginosis, but it is unclear if bacterial vaginosis causes PID. Several studies have assessed specific bacterial vaginosis pathogens, reporting that women with high levels of Gram negative anaerobes in the lower genital tract were at higher risk of PID.[97 166 177] Women with bacterial vaginosis are also at higher risk of incident chlamydia or gonorrhoea infection[180] that could in turn increase risk of ascending infection. However, for these cross-sectional data, the temporal relationship between bacterial vaginosis and acquisition of other STIs or developing PID is not known. Based on available evidence, pathogen-negative PID in this publication could represent a false positive PID diagnosis, PID of another microbial aetiology or associated with a past STI or PID where the cervical infection has cleared.

Chapter 5: Time trends in PID diagnosis in an Australian sexual health clinic

SUBMITTED for publication to *Sexual health* on 10th October 2018 (under review): Goller JL, Fairley CK, De Livera AM, Chen MY, Bradshaw CS, Chow EPF, Guy RJ, Hocking JS. Trends in diagnosis of pelvic inflammatory disease in an Australian sexual health clinic, 2002 to 2016: before and after clinical audit feedback and service improvements.

5.1 Introduction

Chapter 5 addresses objective two of this thesis and investigates time trends in PID diagnosis in an Australian sexual health clinic. It is well known that clinical diagnosis of PID is imprecise and that PID practices can vary between clinicians and health care settings.[44 45] Guidelines recommend that clinicians have a high degree of suspicion and low threshold for initiating PID treatment if suspected in sexually active women presenting with abdominal pain and where other diagnoses are excluded.[13]

Previously, a clinical audit at a large Australian sexual health clinic reported variability in PID diagnosis rates between doctors and concluded that some PID cases were likely to have been missed.[44] After the audit, doctors were given feedback and some actions were undertaken that sought to improve consistency of PID diagnosis between doctors, and to increase PID diagnosis rates. To date, there has been no assessment whether PID diagnosis trends have altered following this audit.

Chapter 5 presents findings from an analysis of Australian sexual health clinic data that investigated PID diagnosis characteristics and trends over time before and after audit feedback. A manuscript of the findings has been prepared and submitted to the journal *Sexual Health* and is currently under review. The methods used in this chapter are detailed in the following manuscript. In brief, yearly rates of first PID diagnosis for women aged 16-49 years attending the sexual health clinic between 2002 and 2016 were calculated. Multivariable generalized linear mixed models; adjusting for patient risk and an STI (chlamydia, gonorrhoea, *M. genitalium*) and/or bacterial vaginosis diagnosis; and, stratified by the period before and after feedback; were used to assess if PID rates changed over time, accounting for between-doctor variability.

TITLE: Trends in diagnosis of pelvic inflammatory disease in an Australian sexual health clinic, 2002 to 2016: before and after clinical audit feedback

Authors: Goller JL, Fairley CK, De Livera AM, Chen MY, Bradshaw CS, Chow EPF, Guy RJ, Hocking JS.

ABSTRACT

Background: An audit of PID diagnosis rates in an Australian sexual health clinic in 2006 found variability between doctors. Doctors were given audit feedback toward increasing PID detection and reducing variability. The clinic implemented other improvements to increase capacity. This study investigated PID diagnosis trends over time before and after audit feedback.

Methods: Yearly rates of first PID diagnosis for women 16-49 years attending Melbourne Sexual Health Centre (2002-2016) were calculated. Multivariable generalized linear mixed models; adjusting for patient risk and sexually transmitted infection (STI) (chlamydia, gonorrhoea, *Mycoplasma genitalium*) and/or bacterial vaginosis (BV) diagnosis; and, stratified by before (July2002-June2007) and after (July 2007-June2016) feedback; were used to assess if PID rates changed over time, accounting for between-doctor variability.

Results: During the study-period, 144 doctors undertook 84,476 female consultations and diagnosed 1755 (2.1%, 95%CI: 2.0-2.2) with PID. Comparing 2002-03 to 2015-16, the yearly PID rate increased from 0.8% (37/4836) to 2.9% (209/7088), and comparing before and after-feedback, a higher proportion of women reported any symptoms at triage (35.1% to 47.2%or had STI/ BV diagnosed (10.1% to 14.9%). After feedback, univariable analysis showed PID rates increased by 8% yearly (incidence rate ratio, IRR 1.08, 95%CI: 1.06-1.11), but, were unchanged (aIRR 1.01, 95%CI: 0.98-1.03) after adjustment for patient characteristics. Factors associated with PID were self-report of any symptoms at triage, age (16-29 years), and an STI/BV diagnosis. Lower variability in doctor-specific rates was observed after-feedback.

Conclusion: Increasing rates of PID diagnosis were driven by an increasing risk profile of female patients.

Introduction

Pelvic inflammatory disease (PID) is an inflammatory disorder of the female upper genital tract that occurs following infection ascent from the lower genital tract.(1, 2) The sexually transmitted infections (STIs) Chlamydia trachomatis (chlamydia), Neisseria gonorrhoea (gonorrhoea)(2-4) and Mycoplasma genitalium (MG) are known PID causes(5) and there is a strong association with bacterial vaginosis (BV).(6)

Pelvic pain is a key characteristic of PID. Other features can include abnormal vaginal discharge, bleeding or dyspareunia although many women experience no signs or symptoms as infection ascends to the upper genital tract, causing subclinical PID that is diagnosed via laparoscopy.(1) PID can have serious reproductive sequelae including infertility, chronic pelvic pain and ectopic pregnancy.(7, 8) To minimise the risk of such complications, it is important that PID is diagnosed and treated promptly.(9) However, PID is notoriously difficult to diagnose. Most diagnoses are clinically made and there is no objective non-invasive diagnostic test or physical feature both sensitive and specific to PID diagnosis.(1) The presence of one or more of uterine, cervical motion or adnexal tenderness in sexually active women with recent onset pelvic pain are widely used as minimum criteria for initiating PID treatment.(10, 11)

Guidelines recommend that clinicians have a low threshold for PID diagnosis.(10, 11) However, the condition's non-specific nature creates potential for diagnostic inconsistencies. In the United Kingdom, a survey of general practitioners found a fifth of respondents reported PID diagnostic practices that were consistent with a 'gold standard'(12) and in Australia, a clinical audit in remote primary health services found PID was diagnosed in only 16% of presentations meeting PID diagnostic criteria.(13) (14)

A clinical audit, in an Australian sexual health clinic previously identified variability in rates of clinically diagnosed PID between doctors and concluded some PID cases were likely to have been missed.(15) Following the audit(15) the clinic reviewed its PID diagnosis and management procedures and undertook several actions seeking to improve consistency of PID diagnosis between doctors, and to increase PID diagnosis rates. These actions included benchmarking in which doctors received their own PID diagnosis rate compared to the

average, a clinical meeting to discuss the audit results and PID diagnostic criteria, and, addition of a PID checklist used during triage of chlamydia or MG positive women attending for treatment. Gonorrhoea diagnosis among women was infrequent in the clinic at this time.(16) There was no follow up audit at the clinic. The aim of this study was to investigate PID diagnosis trends over time before and after audit feedback, adjusting for patient characteristics.

Methodology

We conducted an analysis of PID diagnosis trends over time using retrospective routinely collected data for female patients aged 16-49 years attending an Australian sexual health clinic between July 2002 and June 2016.

Melbourne Sexual Health Centre (MSHC) is the major public sexual health clinic in the state of Victoria, Australia and provides a free walk-in triage based service.(17) Women reporting high risk behaviour, with symptoms suggesting an STI, or pelvic pain are triaged into the clinic. Patients are seen in the order they are triaged. Symptomatic patients are seen by a doctor and less complicated patients by a nurse or doctor, depending on availability. Doctors include a mix of sexual health physicians and trainees, infectious disease physicians and doctors on placements toward general practitioner or infectious disease training.

Data for each patient attendance are recorded in the electronic medical record (EMR) that collects demographics, self-reported symptoms at triage (e.g. pain, vaginal discharge) and self-reported risk information for first or repeat visits >3 months apart, and, clinician entered data including investigations and diagnoses (selected from a diagnosis code list). Chlamydia testing is routinely offered to all new female patients. Women with suspected PID are also tested for gonorrhoea, BV, and, since 2011 for MG. Female sex-workers attend regularly for health checks that include chlamydia and gonorrhoea testing.

PID diagnosis at MSHC is clinical and guided by local guidelines that are updated routinely to reflect national and international guidelines. The minimum criteria being the presence of cervical motion tenderness or uterine tenderness or adnexal tenderness in young sexually active women or other women at STI risk who are experiencing pelvic or lower abdominal pain and no other cause is identified.(10) These PID diagnostic criteria did not change

markedly throughout the study period. However, before 2002, Centers for Disease Control guidelines recommended PID treatment be commenced where all three features of abdominal, cervical motion and adnexal tenderness were present.(18)

Previously, MSHC undertook a clinical audit for the period July 2002 to June 2006 that showed variable PID diagnosis rates between doctors.(15) The audit results were finalised in the first half of 2007. In late 2007, doctors were provided with written feedback about the audit findings, their own PID diagnosis rate, and, how it compared with the overall rate. The audit results were discussed at a clinical meeting attended by doctors and nurses that highlighted the importance of diagnostic sensitivity rather than specificity, and, the clinic reviewed its PID diagnosis and management guidelines. There was no formal change to the clinic's PID guidelines. In addition, a PID checklist that assessed for presence of pelvic pain, abnormal discharge, deep dyspareunia or abnormal uterine bleeding was added to a clinical assessment proforma used during nurse triage of chlamydia or MG positive patients attending for antibiotic treatment. Women with any of these symptoms were subsequently assessed by a doctor.

For this study, women aged 16-49 years who attended MSHC between July 2002 and June 2016 and were assessed by a doctor were eligible. Demographic, risk [number of male sexual partners (MSP) and condom-use in the past 3 months, STI contact, sex work], and clinical data (test results, diagnosis codes, details of attending doctor) were extracted for eligible women from the EMR. To maximise the number of eligible consultations, risk behaviour information for repeat visits <3 months apart by eligible women was applied from earlier visits where available. PID was the primary outcome and based on a PID diagnosis code, only the first PID diagnosis for any woman was included. Binary variables were created for demographics, risk [unprotected (condomless) sex with non-regular MSP in the past 3 months, STI contact], and, diagnosis of a lower genital infection (chlamydia, gonorrhoea, MG and/or BV) during the current visit. Diagnosis of these infections was based on laboratory results; chlamydia and gonorrhoea by nucleic-acid-amplification from urine, vaginal or endocervical swabs, with microscopy and culture for women testing positive gonorrhoea; MG by polymerase-chain-reaction on urine, vaginal or endocervical swabs; and BV by microscopy, predominantly a

Nugent score of 7-10, or 4-6 with clue-cells. A categorical time variable for each 12-months from July to the following June (e.g. July 2007 to June 2008) was created.

The Alfred Health Human Research Ethics Committee (EC00315) provided study approval.

Statistical analysis

Data were analysed using STATA statistical software, v14.0. Yearly PID diagnosis rates per 100 female consultations by doctor were calculated. Age, self-report of any symptoms at triage, diagnosis of a lower genital tract infection, recent unprotected sex, self-reported STI contact, and sex work were identified a priori as confounders. We used a generalized linear mixed effects model, stratified by the time-period before (July 2002 to June 2007) and after (July 2007 to June 2016) audit feedback to assess if yearly PID diagnosis rates changed linearly over time, with a random-intercept term at doctor level to account for between-doctor variability, and, adjusted for potential confounders in multivariable models. We report incidence rate ratios (IRR) with 95% confidence intervals (95% CI).

Results

Over the 14-year study period, there were 144 doctors who worked at MSHC and undertook 84,476 consultations for women aged 16-49 years, among whom 1755 (2.1%; 95%CI: 2.0-2.2) were diagnosed with PID. For these doctors, the yearly doctor specific PID diagnosis rate ranged from 0% to 13% (median: 1.0, IQR: 0-2.8). The yearly number of PID cases and female consultations and the PID diagnosis rate increased over time; from 0.8% (37/4836) in 2002-03 to 1.7% (100/5828) in 2007-08, up to 2.3% (157/6843) in 2010-11 and then 2.9% (209/7088) in 2015-16 (Figure 1). The characteristics of women assessed by these doctors changed over time (Table 1, Figure 2). Comparing the before and after-feedback periods the proportion of consultations for which a woman reported any symptoms at triage increased from 35.1% to 47.2% or recent unprotected sex from 16.0% to 25.7%. The proportion of female consultations for which an STI or BV was diagnosed was higher in the after-feedback period (14.9%) than before (10.1%) (table 1). After-feedback chlamydia was diagnosed in 4.3 , gonorrhoea in 0.5% and BV in 14.9%of consultations. . For all chlamydia or gonorrhoea diagnoses, 57.1% in the after-feedback period, were in women reporting any symptoms at triage compared to 38.5% before-feedback.

Univariable analyses indicated that, PID diagnosis rates increased by 19% yearly during the before-feedback period (IRR 1.19, 95%CI: 1.10-1.29) and 8% yearly (IRR 1.08, 95%CI: 1.06-1.11) in the after-feedback period (Table 2). Multivariable analyses indicated that PID diagnosis rates during the after-feedback period were unchanged (aIRR 1.01, 95%CI: 0.98-1.03) when adjusted for patient characteristics, while the rates remained the same during the before-feedback period (aIRR 1.19, 95% CI 1.10-1.28). The estimated variances of the random intercept terms between the doctors were 0.62, (95%CI: 0.32-1.22) during the before-feedback period and 0.26, (95%CI: 0.16-0.42) during the after-feedback period. Self-report of any symptoms at triage had the strongest association with a PID diagnosis, and, other factors included younger age (16-29 years), diagnosis of a lower genital tract infection, and, attending the clinic as an STI contact. Self-report of recent unprotected sex was associated with a PID diagnosis in the after-feedback period.

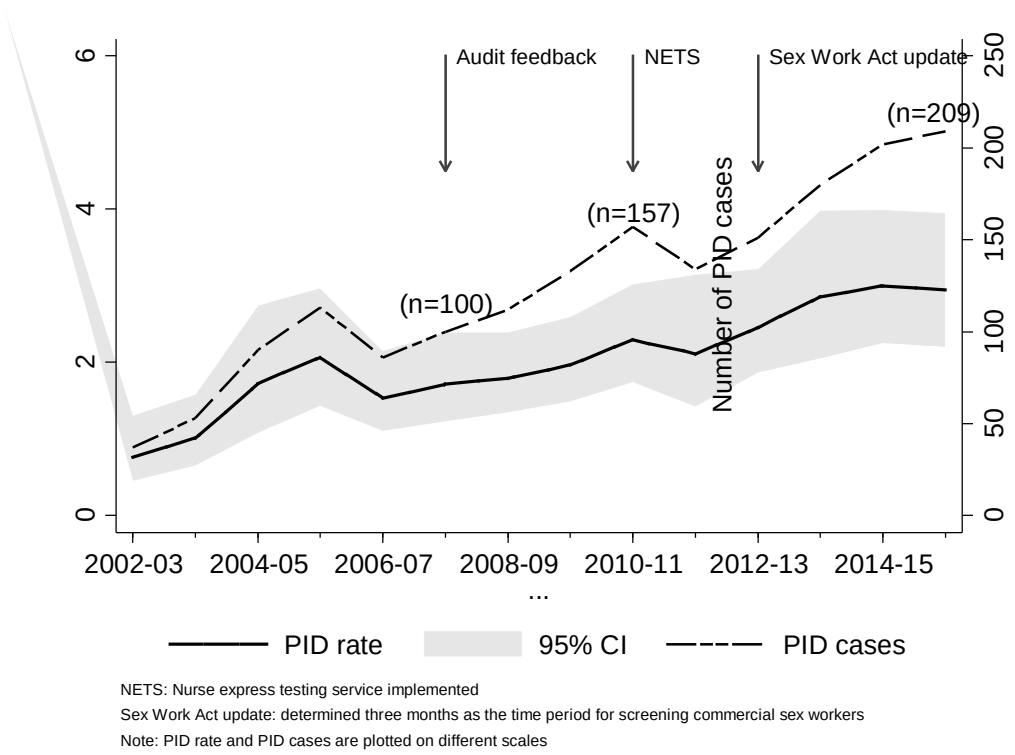
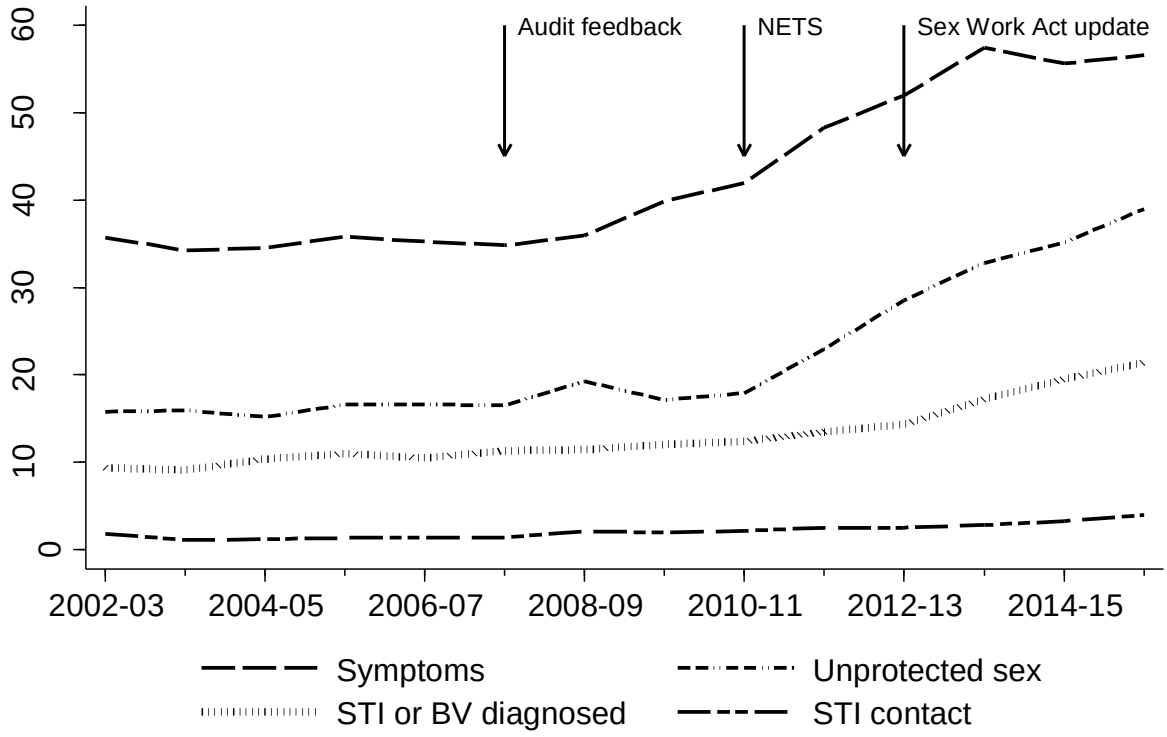


Figure 1: Number of PID cases and PID diagnosis rates, 2002-2016

Table 1: Characteristics of female patients consulted with by doctors before and after audit feedback, 2002-2016

	Before feedback[a]		After feedback[b]	
	n	%	n	%
Total consultations	26194		58282	
PID diagnosed	377	1.4	1378	2.4
Aged 16-29 years	16219	61.9	35708	61.3
Self-reported symptoms at triage	9199	35.1	27478	47.2
Self-reported STI contact	354	1.4	1472	2.5
Current sex worker	4674	17.8	14682	25.2
Unprotected sex with non-regular MSP[d], last 3 months	4199	16.0	14954	25.7
Lower genital tract infection diagnosed[c]	2641	10.1	8680	14.9
Chlamydia diagnosed	760	2.9	2496	4.3
Gonorrhoea diagnosed	36	0.1	274	0.5
MG diagnosed	17	0.1	329	0.6
BV diagnosed	1927	7.4	6199	10.6

a. July 2002 to June 2007; b. July 2007 to June 2016; c. One or more of chlamydia, gonorrhoea, MG or BV diagnosed during this attendance; d. Male sexual partner



NETS: Nurse express testing service implemented

Sex Work Act update: determined three months as the time period for screening commercial sex workers

STI or BV: chlamdia, gonorrhoea, M. genitalium, bacterial vaginosis

Figure 2: Characteristics of female patients, 2002-2016

Table 2: Factors associated with PID diagnosis rates before and after audit feedback, 2002-2016

	Before feedback[a]		After feedback[b]	
	Univariable IRR (95%CI)	**Multivariable aIRR (95%CI)**	**Univariable IRR (95%CI)**	**Multivariable aIRR (95%CI)**
Study time, year	1.19 (1.10-1.29)	1.19 (1.10-1.28)	1.08 (1.06-1.11)	1.01 (0.98-1.03)
Self-reported symptoms				
No	1.0	1.0	1.0	1.0
Yes	4.76 (3.79-5.97)	4.58 (3.57-5.86)	6.24 (5.37-7.25)	5.33 (4.55-6.24)
Patient age				
16-29 years	1.48 (1.18-1.84)	1.35 (1.08-1.69)	1.91 (1.69-2.16)	1.49 (1.31-1.69)
30-49 years	1.0	1.0	1.0	1.0
Lower genital tract infection[c]				
No	1.0	1.0	1.0	1.0
Yes	3.19 (2.55-4.00)	2.10 (1.67-2.65)	2.69 (2.41-3.01)	1.71 (1.52-1.92)
Unprotected sex with non-regular MSP[d], last 3 months				
No	1.0	1.0	1.0	1.0
Yes	1.56 (1.23-1.98)	1.22 (0.96-1.56)	1.89 (1.70-2.11)	1.34 (1.20-1.50)
Current sex worker				
No	1.0	1.0	1.0	1.0
Yes	0.56 (0.41-0.77)	1.03 (0.73-1.43)	0.50 (0.43-0.58)	1.04 (0.88-1.22)
Self-reported STI contact				
No	1.0	1.0	1.0	1.0
Yes	2.21 (1.24-3.93)	4.01 (2.18-7.38)	2.13 (1.68-2.69)	2.01 (1.58-2.55)

a. July 2002 to June 2007; b. July 2007 to June 2016; c. One or more of chlamydia, gonorrhoea, MG or BV diagnosed during this attendance; d. Male sexual partner

Discussion

This study assessed PID diagnosis trends over time before and after audit feedback in a sexual health clinic. Although we found that PID diagnosis rates increased after audit feedback, the increase was explained by a marked increase in the risk profile of female patients assessed by doctors in the clinic. This after-feedback period was also characterised by substantial increases in the yearly number of both female consultations and PID cases diagnosed. We also found that there appeared to be less deviation in doctor-specific rates from overall PID rates in the period following feedback than before.

Our study had several strengths. First, our multivariable analysis accounted for clustering by clinician to account for variable diagnostic practices between doctors over time. Second, inclusion of patient risk factors allowed our multivariable analysis to account for a changing

risk profile of women that impacted on PID diagnosis over the 14-year study period. Our studies main limitation was that we could not verify the accuracy of PID diagnoses or determine the severity of PID cases diagnosed. Standard practice at MSHC is to review PID cases within three days to assess a clinical response to antibiotic treatment. Failure to improve suggests another diagnosis or a need for alternative antibiotics.(19) Although women reporting any symptoms at triage were over five times more likely to be diagnosed with PID, these routinely collected data did not have detail of the severity of signs and symptoms or clinical assessment that supported the clinician to diagnose PID or assess treatment response. However, the characteristics associated with a PID diagnosis were largely consistent with PID guidelines and risk factors.(10, 20)

PID diagnosis is imprecise and diagnostic sensitivity can vary between doctors.(14, 15) In this sexual health clinic, an audit in 2006 identified differences in PID diagnosis rates between doctors and led to actions around a decade ago toward improving consistency of PID diagnostic criteria between doctors. Until this study, there has been no assessment of what happened after the audit response. The discussions following the PID audit centred largely on the merit of being more sensitive versus more specific to a PID diagnosis, with no formal change to the clinic's diagnostic criteria. Doctors were encouraged to reflect on their own diagnostic criteria, on the basis that those who diagnosed PID at a low rate might increase their diagnostic sensitivity. Anecdotally some doctors considered that the benchmarking and discussions helped them to appraise their diagnostic criteria. The PID checklist may have helped identify symptoms suggestive of PID in women returning for STI treatment and for diagnosis of additional PID cases. While, our finding of less PID diagnostic variability after audit feedback suggests some change in clinical practice, it is uncertain whether this was because of the audit. There is a risk that an emphasis on diagnostic sensitivity could come at the expense of specificity. Clinicians who are highly sensitive to PID might diagnose PID in healthy women (over-diagnosis), or, in women with another condition (misdiagnosis) such as appendicitis. A false-positive diagnosis could delay care for another condition, expose women and their sexual partners to STI-related stigma and to unnecessary antibiotic treatment with implications for antimicrobial resistance. The risk of over-diagnosis could be higher for less-experienced doctors. A cross-sectional study in the UK showed PID diagnostic acumen was greater with more clinical experience.(15)

Such diagnostic challenges are not new and have prompted assessment of the clinical criteria that best correlate with upper genital tract infection. A secondary analysis of data for over 600 Swedish obstetrics and gynaecology patients in the 1960s reported that lower abdominal pain had a pretest probability of 79% for laparoscopically diagnosed PID but showed no meaningful difference between pre and post-test probabilities for most signs and symptoms.(21) These uncertainties about PID diagnosis in the Swedish(21) and more recent data(22) highlight the need for a simple test that can accurately diagnose PID. While a range of biomarkers for upper genital tract inflammation are being investigated,(23, 24) objective tests for clinical use are some way off.

In this study, changes in the patient risk profile appear to have had the greatest impact on PID diagnosis rates. Univariable analysis showed that PID rates increased by 8% yearly after audit feedback, but this increase was not apparent after adjusting for patient characteristics in multivariable analysis. The decade since audit feedback involved other changes that may have impacted on PID diagnosis, even if not specifically PID focussed. MSHC is the only full-time and free sexual health service in the Australian state of Victoria, the population of which now exceeds 6 million.(25) As the Victorian population and demand for services grows, the clinic has implemented processes (largely within existing resources) toward improving clinical efficiency while maintaining optimal care. In 2010, MSHC implemented a nurse express testing service,(26) in which asymptomatic heterosexuals at STI risk complete a sexual history, collect their own samples, receive phone results, and reattend the clinic for treatment if positive. This nurse led service has streamlined care for many asymptomatic heterosexual patients and increased capacity for greater numbers of patients including high risk symptomatic patients to attend the clinic. Furthermore, an update to the Victorian Sex Work Act (2012) determined the time period for screening of people in the sex industry as three monthly (previously monthly), thereby reducing sex worker consultations,(27) and, increasing capacity for other patients and STI diagnosis.(28) Female commercial sex workers have had a low STI prevalence in the state of Victoria.(29) In this context of improved clinical efficiencies, doctors in this study undertook an increasing number of female consultations, including for high risk women and diagnosed an additional 52 women with PID in 2015-16 compared with 2010-11.

Population-based sexual behaviour data show increasing numbers of lifetime sex partners for young Australians, potentially increasing their STI risk.(30) This combined with surveillance data that show increasing gonorrhoea rates for women that cannot be explained by increased testing appears to reflect increasing transmission in these populations(31) Chlamydia diagnoses have also increased and although influenced by testing, annual chlamydia testing levels in Australia are low, testing only 15% of 15-29 year-olds in 2016.(31) These increases in sexual risk practices and STIs could translate into increasing PID diagnoses in this and other clinical settings.

So, what are the implications for PID diagnosis in other clinical settings. In the absence of new diagnostics, there is an ongoing need for tools, training and processes that can support clinicians to consider both sensitivity and specificity within PID diagnostic criteria. General practice is an important provider of care for mild to moderate PID in Australia(11, 32) however sexual health care is not core business. Recent Australian data show that less than half of general practitioners (GPs) asked about female pelvic symptoms with STI treatment.(33) The PID checklist used in this clinic is brief and could be a resource to remind GPs of the possibility of PID when treating women with an STI. Other resources developed for Australian general practice include an algorithm for assessing abdominal pain in reproductive age women and a guide to bimanual examination.(34) The challenge is to systematise such resources into routine care. Hyperlinks in positive test results have been used to increase GP access to partner notification resources(35) and could help integrate PID resources into care. This would ideally be complemented by education and training and establishment of indicators to monitor PID diagnosis over time. In this clinic, service improvements that increased capacity for care of more complex patients by doctors and more asymptomatic patients by nurses(26) appeared to have the greatest impact on PID diagnosis. Other strategies involving doctors and nurses have had some success in improving PID diagnosis. A multifaceted intervention in a North American emergency department targeted medical and nursing staff (education, posters of PID treatment guidelines) and patients (written discharge handout) and showed improvements in PID diagnosis, treatment, and, sexual history taking for young women presenting with lower abdominal pain.(36) The potential for models of care that incorporate nurses into sexual health care in general practice could also be explored.

Conclusion

Availability of best practice care is essential for women at risk of PID and STIs. Clinical audit offers a mechanism for improvements in clinical practice and reorientation of services can increase capacity. In this Australian sexual health clinic, it was uncertain whether PID specific actions after a clinical audit led to changes in PID diagnostic sensitivity but service improvements appeared to have had a greater impact on PID trends, providing additional capacity for high-risk patients and an increase in the overall number of PID cases diagnosed and managed.

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5.3 Chapter summary

The study in Chapter 5 investigated long-term PID diagnosis characteristics and trends at a large sexual health clinic, before and after clinical audit feedback. The study found that between 2002 and 2016, 144 doctors undertook 84,476 female consultations and diagnosed 2.1% with PID, with the yearly PID diagnosis rate increasing from 0.8% (37/4836) to 2.9% (209/7088) and an increasing proportion of women reported any symptoms (35.7% to 56.6%) or diagnosed with an STI or bacterial vaginosis (9.4% to 21.4%). After audit feedback in 2007, univariable analysis showed PID rates increased by 8% yearly (incidence rate ratio, IRR 1.08, 95%C: 1.06, 1.11), but, were unchanged (aIRR 1.01, 95%CI 0.98, 1.03) after adjustment for patient characteristics in multivariable analysis. Since audit feedback, the clinic has reoriented services to increase patient capacity including for high risk patients that appear to have had a greater impact on PID diagnosis rates than audit feedback. For example, the clinic introduced a nurse led service in 2010 that streamlined care for asymptomatic heterosexual patients, thereby increasing capacity for more high risk symptomatic patients to attend the clinic.[273]

This was the first analysis of PID time trends in an Australian sexual health clinic. This study highlights the importance of both clinical audit as a mechanism to identify areas for improvements in clinical practice and reorientation of services to improve clinical efficiencies. This Chapter demonstrates the importance of adjustment for patient characteristics in interpreting PID trends.

Chapter 6: Time trends in PID diagnosis in Australian hospitals

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6.1 Introduction

This Chapter addresses the third objective of this thesis, to estimate time trends in PID diagnosis in Australian hospitals. Previous analyses of Australian data have shown declining PID rates in hospital admissions during the 1990s and 2000s.[14 24 238] The most recent national PID rates extend to 2007. Ectopic pregnancy and infertility that occur due to fallopian tube scarring are serious sequelae of PID.[246 247]. Declining ectopic pregnancy rates in Australian hospitals have been reported to as recently as 2007.[14 239]

Since these reported declines, a cluster randomised controlled trial (ACCEPt)[256 264] of a chlamydia testing intervention in Australian primary care clinics was conducted. ACCEPt investigated the effectiveness of annual chlamydia testing for 16-29-year-old women and men in primary care on chlamydia prevalence in the population. A secondary aim was to investigate the effect of the intervention on PID incidence. Toward this objective, hospital admission and emergency department data involving a PID diagnosis were collected. In addition, admission and emergency department data were collected for ectopic pregnancy, and, orchitis or epididymitis for men.

This Chapter presents findings from an ecological study published in *Sexually Transmitted Infections.*[274] Although PID is the outcome of focus in this thesis, ectopic pregnancy rates were investigated in this chapter as another measure of female reproductive tract morbidity. The publication presents an analysis of yearly PID and ectopic pregnancy rates in the three most populous states of Australia (NSW, Victoria and Queensland) for women aged 15-44 years for the period 2009 to 2014. Rates were calculated using routinely collected hospital admission and emergency department attendance data as the numerator, and, population and live birth

denominators. This is the first analysis to include Australian emergency department data toward a measure of these outcomes. The methods used in this chapter are detailed in the following publication. In brief, univariable and multivariable Poisson regression models were used to examine variation in PID and ectopic pregnancy rates by year, age-group and remoteness and socio-economic disadvantage of residential area. A stratified analysis of PID admission rates was conducted by PID category, being chlamydia or gonorrhoea related PID, acute PID, unspecified PID and chronic PID. Further detail of the data sources, a breakdown of the annual number of cases and coding sensitivity analyses and sensitivity analysis findings were published as additional material that was published online only and are provided in Appendix 2.

ORIGINAL ARTICLE

Rates of pelvic inflammatory disease and ectopic pregnancy in Australia, 2009–2014: ecological analysis of hospital data

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ABSTRACT

Objective To analyse yearly rates of pelvic inflammatory disease (PID) and ectopic pregnancy (EP) diagnosed in hospital settings in Australia from 2009 to 2014.

Methods We calculated yearly PID and EP diagnosis rates in three states (Victoria, New South Wales, Queensland) for women aged 15–44 years using hospital admissions and emergency department (ED) attendance data, with population and live birth denominators. We stratified PID diagnoses as chlamydial-related or gonorrhoeal-related (*Chlamydia trachomatis* (CT)-related or *Neisseria gonorrhoeae* (NG)-related), acute, unspecified and chronic, and analysed variations by year, age and residential area using Poisson regression models.

Results For PID, the rate of all admissions in 2014 was 63.3 per 100 000 women (95% CI 60.8 to 65.9) and of all presentations in EDs was 97.0 per 100 000 women (95% CI 93.9 to 100.2). Comparing 2014 with 2009, the rate of all PID admissions did not change, but the rate of all presentations in EDs increased (adjusted incidence rate ratio (aIRR) 1.34, 95% CI 1.24 to 1.45), and for admissions by PID category was higher for CT-related or NG-related PID (aIRR 1.73, 95% CI 1.31 to 2.28) and unspecified PID (aIRR 1.09, 95% CI 1.00 to 1.19), and lower for chronic PID (aIRR 0.84, 95% CI 0.74 to 0.95). For EP, in 2014 the rate of all admissions was 17.4 (95% CI 16.9 to 17.9) per 1000 live births and of all ED presentations was 15.6 (95% CI 15.1 to 16.1). Comparing 2014 with 2009, the rates of all EP admissions (aIRR 1.06, 95% CI 1.04 to 1.08) and rates in EDs (aIRR 1.24, 95% CI 1.18 to 1.31) were higher.

Conclusions PID and EP remain important causes of hospital admissions for female STI-associated complications. Hospital EDs care for more PID cases than inpatient departments, particularly for young women. Updated primary care data are needed to better understand PID epidemiology and healthcare usage.

INTRODUCTION

Chlamydia trachomatis (CT) and *Neisseria gonorrhoeae* (NG) can ascend to the upper genital tract and have serious health consequences for women, including pelvic inflammatory disease (PID), which can lead to ectopic pregnancy (EP), chronic pelvic pain or infertility,[1 2] which may be unrecognised until affected women try to conceive. These sequelae account for substantial healthcare costs,[3] and their prevention is an important reason for STI control policies.[4]

In many countries including Australia, PID and EP are not statutorily notifiable, but data sets about diagnoses in hospitals provide information about rates over time. The gonorrhoea epidemics in many industrialised countries during the 1960s and 1970s were associated with increasing PID incidence followed by increasing EP incidence.[5] From the 1980s to 2010, declining PID rates in hospital admissions and general practice were reported in several countries including Australia,[5–14] with some reports suggesting declines were influenced by STI control.[12] However, in the 1980s and 1990s, falls in PID and STIs were also attributed to sexual behaviour changes in response to the HIV epidemic.[6] Stable or declining EP rates have been reported during the 1990s and 2000s in some countries,[7–9] but increasing rates have also been reported.[10]

In 2007 in Australia, the hospital admission rate for PID was 89 per 100 000 population and EP was 16 per 1000 live births among women aged 15–39 years.[8] Since then, chlamydia and gonorrhoea diagnosis patterns have changed. Among women, age-standardised chlamydia diagnosis rates increased from 2007 to 2011, were stable to 2015, then increased in 2016.[15] Although gonorrhoea occurs predominantly among men who have sex with men, notification rates in women more than doubled from 2007 to 2016, raising concerns about potential reproductive tract complications.[15] The primary objective of this study was to analyse yearly rates of PID and EP diagnosed in Australian hospital settings. The secondary objective was to examine associations between PID or EP diagnosis and characteristics of residential area.

METHODS

We undertook an ecological study using data on the number of hospital admissions and emergency department (ED) attendances for PID and EP in the three most populous Australian states: New South Wales, Victoria and Queensland.

We obtained data from state Departments of Health from separate hospital admissions and ED attendances registers (online supplementary table 1). We received non-identifiable, line-listed

Table 1 Number of hospital admissions and ED presentations for PID and EP, and age breakdown of the population and live birth denominators, by year, 2009–2014

	2009	2010	2011	2012	2013	2014	Overall
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	N (%)
PID*							
Total admissions	2141	2314	2510	2429	2502	2375	**14 271 (100)**
CT-related or NG-related PID†	81 (3.8)	126 (5.4)	123 (4.9)	141 (5.8)	157 (6.3)	142 (6.0)	770 (5.4)
Acute PID‡	124 (5.8)	140 (6.1)	176 (7.0)	151 (6.2)	152 (6.1)	152 (6.4)	895 (6.3)
Unspecified PID§	1379 (64.4)	1513 (65.4)	1674 (66.7)	1614 (66.4)	1613 (64.5)	1592 (67.0)	9385 (65.8)
Chronic PID¶	557 (26.0)	535 (23.1)	537 (21.4)	523 (21.5)	580 (23.2)	489 (20.6)	3221 (22.6)
Total ED presentations	2566	2971	3438	3838	4067	3642	**20 522 (100)**
Admitted from ED	746 (29.1)	837 (28.2)	1054 (30.7)	1172 (30.5)	1375 (33.8)	1298 (35.6)	6482 (31.6)
Not admitted from ED	1820 (70.9)	2134 (71.8)	2384 (69.3)	2666 (69.5)	2692 (66.2)	2344 (64.4)	14 040 (68.4)
Ectopic pregnancy**							
Total admissions	3870	3768	3981	3841	4072	4047	**23 579 (100)**
Total ED presentations	2974	2840	2996	3394	3549	3629	**19 382 (100)**
Admitted from ED	2325 (78.2)	2233 (78.6)	2365 (78.9)	2657 (78.3)	2800 (78.9)	2785 (76.7)	15 165 (78.2)
Not admitted from ED	649 (21.8)	607 (21.4)	631 (21.1)	737 (21.7)	749 (21.1)	844 (23.3)	4217 (21.8)
Denominator/s							
Estimated residential population†† (N)	3 534 785	3 578 562	3 611 095	3 659 865	3 708 538	3 754 048	
15–24 years (%)	32.2	32.1	33.8	31.6	31.4	31.2	
25–34 years (%)	33.4	33.7	34.0	34.2	34.8	35.2	
35–44 years (%)	34.4	34.2	34.2	34.0	33.8	33.5	
Live births‡‡ (N)	234 821	235 805	233 193	239 145	237 205	232 553	
15–24 years (%)	18.0	17.6	17.0	16.9	16.3	15.2	
25–34 years (%)	58.9	59.0	59.9	60.4	60.9	60.6	
35–44 years (%)	23.1	23.4	23.1	22.7	22.8	22.1	

*PID, International Classification of Diseases (ICD-10) codes N70.0, N70.1, N70.9, N71.0, N71.1, N71.9, N73.0, N73.1, N73.2, N73.3, N73.4, N73.5, N73.8, N73.9, (N74.4+A56.1), (N74.3+A54.2).
†CT-related or NG-related PID, ICD-10 codes (chlamydial PID N74.4+A56.1 and gonococcal PID N74.3+A54.2).
‡Acute PID, ICD-10 codes N70.0, N71.0, N73.0.
§Unspecified PID, ICD-10 codes N70.9, N71.9, N73.2, N73.5, N73.8, N73.9.
¶Chronic PID, ICD-10 codes N70.1, N71.1, N73.1, N73.4.
**Ectopic pregnancy, ICD-10 codes O00.0, O00.1, O00.2, O00.8, O00.9.
††Estimated residential population for women aged 15–44 years in 1678 study postcodes.
‡‡Live births, maternal age 15–44 years.
CT, *Chlamydia trachomatis*; ED, emergency department; EP, ectopic pregnancy; NG, *Neisseria gonorrhoeae*; PID, pelvic inflammatory disease.

records for female patients aged 15–44 years old during 2009–2014. Hospital admission data sets included data from all public (government-funded) and private hospitals. ED data sets included data for presentations to public hospitals with a designated ED. Data reporting from EDs was voluntary and clinicians assigned diagnosis codes, making ED data more variable than admissions data. ED attendances can result in discharge or hospital admission, the latter also counted in admissions data sets, but we could not merge these data sets owing to de-identified records and different data systems.

Each patient record included a principal diagnosis for the main reason for care and 'other' diagnoses made, each coded using the International Classification of Diseases 10th Revision, Australian Modification (ICD)-10-AM, or for some EDs the ICD-9 or Systematized Nomenclature of Medicine. Data items included year, age group, residential postcode and principal diagnosis code on which a PID or EP diagnosis was assigned (table 1, online supplementary table 2). Like other Australian studies,[7 8] we excluded records with an 'other' PID or EP diagnosis because they might represent pre-existing conditions. We categorised PID admissions further as chlamydial-related or gonorrhoeal-related (CT-related or NG-related PID), acute PID, PID unspecified or chronic PID. As this analysis focused on trends, we only included ED records from hospitals contributing data in all years and if annual presentation numbers varied by <50%.

Denominator data were obtained from the Australian Bureau of Statistics (online supplementary table 1). At postcode level these included estimated female residential population by year, age, remoteness and Index of Relative Socioeconomic Disadvantage (IRSD).[16] Like another Australian study,[8] we obtained the number of live births by maternal age and year for our EP denominator. The three states comprised 1738 postcodes. Postcodes were excluded (n=18) if the population was zero (eg, company postcodes) or offshore island/s; or recoded to a neighbouring postcode (n=42) if IRSD was unavailable or the population for some age groups was zero (eg, remote postcodes). The remaining 1678 postcodes were categorised for remoteness (metropolitan, inner regional, outer regional and/or remote using standard definitions) and deciles of increasing socioeconomic disadvantage based on the IRSD.

We prepared three data sets. The all-admissions and all-ED data sets included all hospital admissions or ED presentations with a principal PID or EP diagnosis, and population by postcode, year and age group. The non-admitted-ED data set was a subset comprising PID or EP episodes discharged from EDs without admission.

Statistical analysis

We analysed data sets separately using Stata V.14. We calculated yearly PID and EP rates per 100 000 women using population denominators and EP rates per 1000 live births. We examined variation in rates by year, age group, remoteness and socioeconomic disadvantage of postcode using univariable and multivariable Poisson regression models with clustered sandwich estimator to account for intragroup correlation.[17] We included year as a categorical variable to see whether rates differed from the reference category of 2009. We report incidence rate ratios with 95% CI. Where necessary, we used zero-inflated Poisson (ZIP) regression to account for large numbers of postcodes with no cases, and compared the fit with ordinary Poisson models using the Vuong test.[18] Using likelihood ratio tests, we investigated interactions between residential area and age group and reported them if statistically and clinically meaningful. We conducted a subgroup analysis of admission rates by PID category. Two sensitivity analyses were undertaken to examine the robustness of our results. The first used linear splines to explore the rate of change in overall rates per 2-year period. The second repeated our analysis of population rates, omitting postcodes recoded to neighbouring postcodes.

RESULTS

From 2009 to 2014 we recorded a total of 14 271 admissions and 20 522 ED presentations with a principal PID diagnosis, and 23 579 admissions and 19 382 ED presentations with a principal EP diagnosis, across 1678 postcodes (table 1, online supplementary table 2). The median population of women aged 15–44 years old in study postcodes in 2009 was 946 (IQR 212–3254). Two-fifths (42%) of postcodes were metropolitan (representing 76% of the population), 29% in outer regional/remote areas (7% of the population) and 41% of the population lived in more disadvantaged (five most disadvantaged IRSD deciles) areas.

Pelvic inflammatory disease

Two-thirds (65.8%) of PID hospital admissions were unspecified PID, and the remainder were chronic PID (22.6%), acute PID (6.3%), CT-related PID (5.3%) and NG-related PID (0.1%). Most (93.7%) PID in EDs were unspecified PID, and the remainder were acute PID (6.0%), chronic PID (0.1%) and CT-related PID (0.2%). One-third (32%) of PID in EDs resulted in hospital admission (table 1).

Figure 1A and online supplementary table 3 show the annual PID rates per 100 000 women. The overall PID admission rate increased from 60.6 in 2009 to 69.5 in 2011, then decreased to 63.3 in 2014. Between 2009 and 2014, the overall PID rate in EDs increased from 72.6 to 97.0. In multivariable analysis (table 2) comparing 2014 with 2009, the rate of all PID admissions did not change (aIRR 1.05, 95% CI 0.98 to 1.12), but within PID categories (table 3) were higher for CT-related or NG-related PID (aIRR 1.73, 95% CI 1.31 to 2.28) and unspecified PID (aIRR 1.09, 95% CI 1.00 to 1.19), similar for acute PID and lower for chronic PID (aIRR 0.84, 95% CI 0.74 to 0.95). PID admission rates were higher for women aged 15–24 than those aged 35–44 years (aIRR 1.09, 95% CI 1.04 to 1.14), including CT-related or NG-related PID (aIRR 11.68, 95% CI 8.60 to 15.85) and unspecified PID. Chronic PID admission rates were highest for women aged 35–44 years. In EDs, overall PID rates were higher in 2014 than in 2009 (aIRR 1.34, 95% CI 1.24 to 1.45), including PID managed without admission, and were more than twice as high for women aged 15–34 than those aged 35–44 years. Higher PID rates were observed in more disadvantaged and non-metropolitan (regional or remote) than metropolitan areas.

Ectopic pregnancy

The most frequent EP diagnoses codes were O00.1 tubal pregnancy (70% of admissions) and O00.9 EP unspecified (83% of ED), and 78% of EPs in EDs resulted in hospital admission. Yearly population rates of EP are shown in figure 1B and online supplementary table 3 and EP rates among live births in figure 1C.

Population rates

The overall EP hospital admission rate per 100 000 women in 2014 was 107.8 and did not differ from 2009 (table 2). Between 2009 and 2014, EP rates in EDs increased overall (84.1–96.7) and for women discharged without admission (18.4–22.5).

In multivariable analysis (table 2), comparing 2014 with 2009, EP rates in hospital admissions did not change but were higher in EDs (aIRR 1.12, 95% CI 1.05 to 1.20). Admission and ED rates were highest for women aged 25–34 compared with those aged 35–44 years and in more disadvantaged and non-metropolitan areas. The rates of EP discharged from EDs without admission were higher in 2014 than in 2009 (aIRR 1.17, 95% CI 1.00 to 1.37) and lowest in the outer regional/remote areas (aIRR 0.69, 95% CI 0.49 to 0.96).

Live birth rates

Overall EP rates per 1000 live births in 2014 were 17.4 in admissions, 15.6 in EDs and 3.6 for EDs but not admitted. In multivariable analysis, EP admission rates (table 2) were higher in 2014 than in 2009 (aIRR 1.06, 95% CI 1.04 to 1.08) and highest for women aged 35–44 years. In EDs, EP rates were highest for women aged 15–24 years and in 2014 compared with 2009 (aIRR 1.24, 95% CI 1.18 to 1.3).

Sensitivity analyses

Linear splines showed the rate of change for population rates did not alter during the study, and the rate of change for ED-EP live birth rates during 2011–2012 was higher than for 2009–2010 (online supplementary table 4). Omission of postcodes recoded to neighbouring postcodes showed negligible change to results (data available on request).

DISCUSSION

This ecological study found that for women of reproductive age, overall PID admission rates were similar between 2009 and 2014. Within PID categories, admission rates increased for CT-related or NG-related PID and unspecified PID, but declined for chronic PID. PID rates in EDs increased and were 2.7 times higher among women aged 15–24 than those aged 35–44 years. Age variability in overall PID admission rates was less pronounced. EP rates among live births were higher in 2014 compared with 2009 in admissions and EDs.

Strengths and weaknesses

Our study had two main strengths. First, inclusion of ED data provided new information about PID and EP diagnoses in Australia, and like other studies[7 8] included public and private hospital admissions for a complete picture of PID and EP admissions. PID rates for women admitted from EDs showed a similar pattern between the admissions and ED data sets. Second, undertaking our analysis at the postcode level allowed exploration of the relationship between area characteristics and

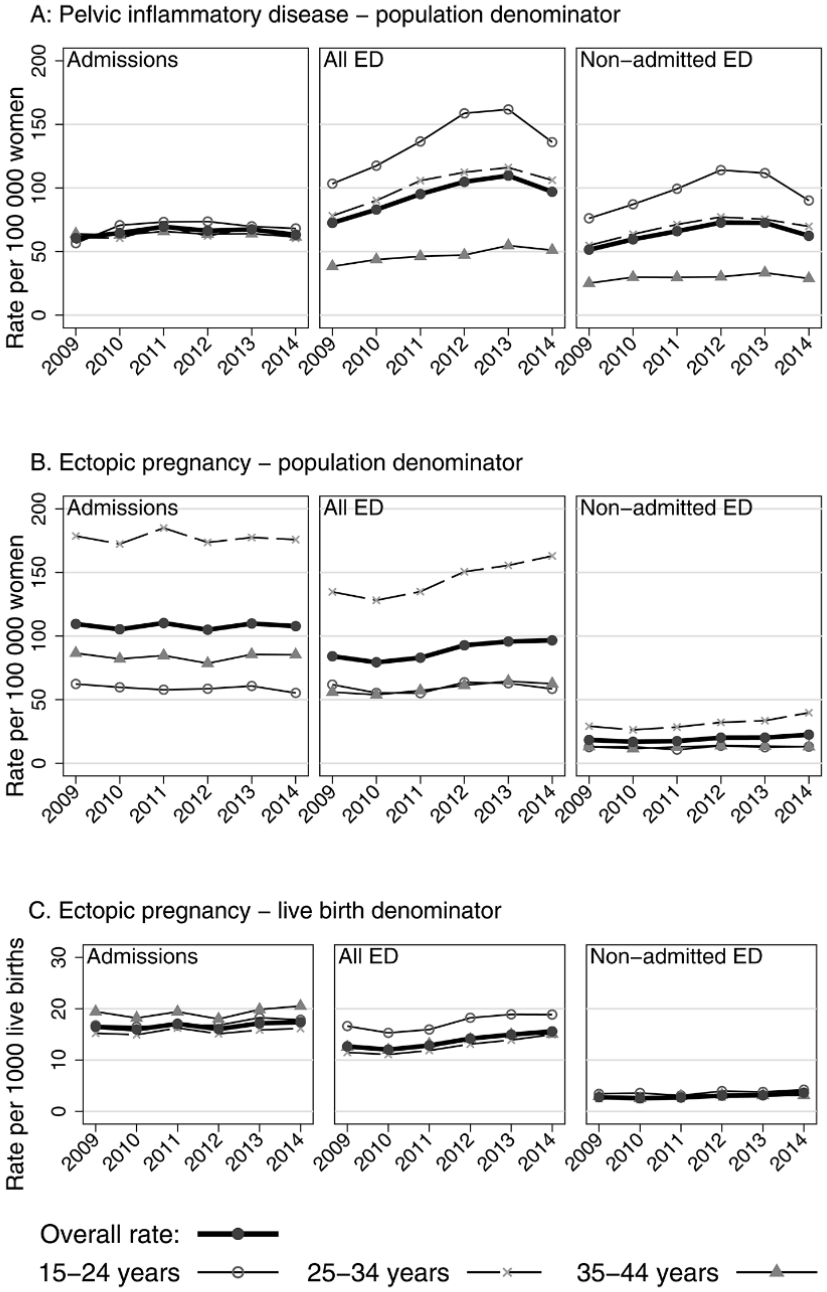

Figure 1 Overall and age-specific admission, emergency department (ED) presentation and non-admitted ED presentation rates of pelvic inflammatory disease and ectopic pregnancy, 2009–2014. (A) Pelvic inflammatory disease, (B) ectopic pregnancy presentation rates per 100 000 women and (C) ectopic pregnancy rates per 1000 live births.

population rates. Large numbers of postcodes with no diagnoses were accommodated by the multivariable ZIP analysis for which our findings were consistent with ordinary Poisson models.

An important study limitation is that our PID rates included only women managed in hospitals. Australian guidelines recommend inpatient management for severe PID and outpatient management for mild-moderate PID.[19] While admissions data can tell us about severe PID, most mild-moderate PID are managed in primary care,[20] general practice being Australia's mainstream primary care setting. Primary care data are needed for a more complete picture of PID, but are not routinely available. Second, because ED data provision is voluntary, we consider our admission data more reliable than ED data. We minimised variability in ED rates by limiting our analysis to EDs contributing data for all study years and with high completeness. Third, clinical PID diagnosis has low sensitivity and specificity compared with laparoscopic visualisation.[2] Absolute diagnosis rates might be inaccurate, but if diagnostic practices were unchanged these trends should be reliable. Uterine, cervical motion and adnexal tenderness in sexually active women with pelvic pain are the mainstay

Table 2 Factors associated with population rates of (A) PID, (B) ectopic pregnancy and (C) ectopic pregnancy rates per 1000 live births, 2009–2014

	All admissions				All emergency department				Non-admitted emergency department			
	Univariable		Multivariable		Univariable		Multivariable		Univariable		Multivariable	
	IRR	(95% CI)	aIRR	(95% CI)	IRR	(95% CI)	aIRR	(95% CI)	IRR	(95% CI)	aIRR	(95% CI)
(A) PID												
Age group in years												
15–24	1.11	(1.05 to 1.16)	1.09	(1.04 to 1.14)	2.78	(2.62 to 2.94)	2.72	(2.57 to 2.87)	3.12	(2.92 to 3.34)	3.02	(2.84 to 3.22)
25–34	1.02	(0.97 to 1.07)	1.01	(0.96 to 1.06)	2.09	(1.98 to 2.21)	2.11	(2.00 to 2.23)	2.25	(2.11 to 2.40)	2.26	(2.12 to 2.41)
35–44	1.0		1.0		1.0		1.0		1.0		1.0	
Area of residence												
Metropolitan	1.0		1.0		1.0		1.0		1.0		1.0	
Inner regional	1.23	(1.17 to 1.29)	1.12	(1.07 to 1.18)	1.63	(1.51 to 1.75)	1.46	(1.36 to 1.56)	1.72	(1.58 to 1.87)	1.53	(1.41 to 1.65)
Outer regional/remote	1.75	(1.63 to 1.87)	1.57	(1.47 to 1.69)	2.28	(2.02 to 2.57)	2.08	(1.87 to 2.32)	2.26	(1.96 to 2.60)	2.06	(1.81 to 2.34)
Socioeconomic status of area												
Deciles of increasing disadvantage	1.06	(1.05 to 1.07)	1.05	(1.04 to 1.06)	1.09	(1.08 to 1.10)	1.07	(1.06 to 1.08)	1.09	(1.08 to 1.10)	1.08	(1.07 to 1.09)
Year												
2009	1.0		1.0		1.0		1.0		1.0		1.0	
2010	1.07	(1.00 to 1.15)	1.07	(1.00 to 1.15)	1.13	(1.04 to 1.23)	1.13	(1.05 to 1.22)	1.13	(1.02 to 1.24)	1.14	(1.04 to 1.24)
2011	1.14	(1.07 to 1.23)	1.14	(1.07 to 1.22)	1.32	(1.21 to 1.45)	1.32	(1.22 to 1.42)	1.30	(1.18 to 1.44)	1.29	(1.18 to 1.41)
2012	1.09	(1.01 to 1.16)	1.09	(1.02 to 1.16)	1.42	(1.30 to 1.55)	1.41	(1.31 to 1.53)	1.39	(1.26 to 1.54)	1.40	(1.28 to 1.53)
2013	1.12	(1.04 to 1.20)	1.12	(1.05 to 1.20)	1.48	(1.36 to 1.62)	1.50	(1.39 to 1.62)	1.37	(1.24 to 1.52)	1.40	(1.28 to 1.53)
2014	1.04	(0.97 to 1.12)	1.05	(0.98 to 1.12)	1.33	(1.22 to 1.45)	1.34	(1.24 to 1.45)	1.22	(1.11 to 1.35)	1.22	(1.12 to 1.33)
(B) Ectopic pregnancy (population rates)												
Age group in years												
15–24	0.72	(0.69 to 0.76)	0.70	(0.67 to 0.74)	1.03	(0.97 to 1.10)	1.00	(0.95 to 1.06)	0.95	(0.82 to 1.09)	0.95	(0.83 to 1.09)
25–34	2.05	(1.98 to 2.13)	2.04	(1.96 to 2.12)	2.33	(2.21 to 2.45)	2.32	(2.20 to 2.44)	2.10	(1.84 to 2.40)	2.08	(1.82 to 2.38)
35–44	1.0		1.0		1.0		1.0		1.0		1.0	
Area of residence												
Metropolitan	1.0		1.0		1.0		1.0		1.0		1.0	
Inner regional	1.12	(1.06 to 1.19)	1.16	(1.10 to 1.22)	1.16	(1.08 to 1.24)	1.16	(1.09 to 1.23)	0.84	(0.69 to 1.03)	0.91	(0.75 to 1.11)
Outer regional/remote	1.46	(1.35 to 1.59)	1.43	(1.32 to 1.55)	1.19	(1.09 to 1.31)	1.13	(1.04 to 1.24)	0.64	(0.45 to 0.92)	0.69	(0.49 to 0.96)
Socioeconomic status of area												
Deciles of increasing disadvantage	1.03	(1.02 to 1.04)	1.03	(1.03 to 1.04)	1.05	(1.04 to 1.06)	1.05	(1.04 to 1.06)	1.01	(1.00 to 1.03)	1.02	(1.00 to 1.04)
Year												
2009	1.0		1.0		1.0		1.0		1.0		1.0	
2010	0.97	(0.91 to 1.03)	0.97	(0.92 to 1.02)	0.96	(0.89 to 1.03)	0.95	(0.89 to 1.02)	0.93	(0.79 to 1.10)	0.94	(0.80 to 1.10)
2011	1.01	(0.95 to 1.07)	1.01	(0.95 to 1.06)	0.98	(0.91 to 1.05)	0.97	(0.91 to 1.04)	0.92	(0.79 to 1.06)	0.92	(0.80 to 1.06)
2012	0.96	(0.91 to 1.03)	0.96	(0.90 to 1.01)	1.12	(1.04 to 1.20)	1.09	(1.02 to 1.17)	1.08	(0.93 to 1.27)	1.07	(0.92 to 1.25)
2013	1.01	(0.95 to 1.08)	1.00	(0.94 to 1.06)	1.14	(1.05 to 1.22)	1.12	(1.04 to 1.20)	1.08	(0.92 to 1.27)	1.08	(0.92 to 1.25)
2014	1.00	(0.94 to 1.06)	0.97	(0.92 to 1.03)	1.14	(1.06 to 1.24)	1.12	(1.05 to 1.20)	1.23	(1.04 to 1.44)	1.17	(1.00 to 1.37)
(C) Ectopic pregnancy (rates among live births)*												
Age group in years												
15–24	0.89	(0.85 to 0.93)	0.89	(0.87 to 0.91)	1.27	(1.15 to 1.40)	1.27	(1.24 to 1.31)	1.23	(0.83 to 1.83)	1.24	(0.83 to 1.83)
25–34	0.81	(0.77 to 0.85)	0.81	(0.80 to 0.83)	0.94	(0.84 to 1.05)	0.94	(0.92 to 0.95)	0.94	(0.62 to 1.42)	0.93	(0.62 to 1.40)
35–44	1.0		1.0		1.0		1.0		1.0		1.0	
Year												
2009	1.0		1.0		1.0		1.0		1.0		1.0	
2010	0.97	(0.83 to 1.14)	0.97	(0.95 to 0.99)	0.95	(0.77 to 1.17)	0.95	(0.92 to 0.98)	0.93	(0.49 to 1.78)	0.93	(0.49 to 1.76)
2011	1.04	(0.89 to 1.20)	1.04	(1.00 to 1.07)	1.01	(0.83 to 1.24)	1.02	(0.98 to 1.05)	0.98	(0.53 to 1.80)	0.98	(0.54 to 1.79)
2012	0.97	(0.84 to 1.14)	0.98	(0.95 to 1.00)	1.12	(0.91 to 1.38)	1.13	(1.09 to 1.16)	1.12	(0.63 to 2.00)	1.12	(0.63 to 1.97)
2013	1.04	(0.88 to 1.24)	1.04	(1.02 to 1.07)	1.18	(0.97 to 1.44)	1.19	(1.15 to 1.22)	1.14	(0.63 to 2.06)	1.15	(0.64 to 2.05)
2014	1.06	(0.89 to 1.25)	1.06	(1.04 to 1.08)	1.23	(1.03 to 1.47)	1.24	(1.18 to 1.31)	1.31	(0.71 to 2.44)	1.32	(0.71 to 2.45)

*Level of socioeconomic disadvantage and remoteness of area were not included as variables in the analysis of ectopic pregnancy rates among live births because these denominator data were not available at postcode level.
aIRR, adjusted incidence rate ratio; IRR, incidence rate ratio; PID, pelvic inflammatory disease.

of PID diagnosis,[2] and until non-invasive biomarkers for upper genital tract inflammation are widely available[2] large-scale diagnostic changes that affect estimated rates are unanticipated. However, current policies promote opportunistic chlamydia testing[4] and could contribute to identifying more STI-associated PID cases. Fourth, our birth denominator did not include all conceptions and EP rates could be influenced by other pregnancy outcomes (eg, stillbirths, abortion) over time. We could

Table 3 Factors associated with PID admissions, by PID category, 2009–2014

	CT-related or NG-related PID		Acute PID		Unspecified PID		Chronic PID	
	aIRR	(95% CI)	aIRR	(95% CI)	aIRR	(95% CI)	aIRR	(95% CI)
Age group in years								
15–24	11.68	(8.60 to 15.85)	0.74	(0.62 to 0.89)	1.46	(1.38 to 1.55)	0.20	(0.18 to 0.23)
25–34	2.95	(2.11 to 4.13)	0.93	(0.78 to 1.10)	1.18	(1.12 to 1.25)	0.69	(0.64 to 0.75)
35–44	1.0		1.0		1.0		1.0	
Area of residence								
Metropolitan	1.0		1.0		1.0		1.0	
Inner regional	0.88	(0.71 to 1.08)	1.31	(1.09 to 1.58)	1.13	(1.06 to 1.20)	1.10	(1.00 to 1.22)
Outer regional/remote	1.56	(1.24 to 1.96)	1.78	(1.43 to 2.22)	1.68	(1.54 to 1.83)	1.11	(0.97 to 1.27)
Socioeconomic status of area								
Deciles of increasing disadvantage	1.08	(1.05 to 1.11)	1.06	(1.03 to 1.09)	1.06	(1.05 to 1.07)	1.01	(1.00 to 1.03)
Year								
2009	1.0		1.0		1.0		1.0	
2010	1.56	(1.18 to 2.07)	1.08	(0.84 to 1.40)	1.09	(1.00 to 1.18)	0.96	(0.85 to 1.09)
2011	1.52	(1.15 to 2.01)	1.36	(1.06 to 1.75)	1.19	(1.09 to 1.29)	0.94	(0.83 to 1.06)
2012	1.72	(1.31 to 2.52)	1.18	(0.92 to 1.52)	1.12	(1.03 to 1.22)	0.92	(0.81 to 1.04)
2013	1.89	(1.44 to 2.47)	1.17	(0.91 to 1.52)	1.12	(1.03 to 1.22)	1.00	(0.88 to 1.13)
2014	1.73	(1.31 to 2.28)	1.15	(0.89 to 1.50)	1.09	(1.00 to 1.19)	0.83	(0.73 to 0.95)

aIRR, adjusted incidence rate ratio; CT-related or NG-related PID, chlamydial (*Chlamydia trachomatis*) or gonococcal (*Neisseria gonorrhoeae*) PID; PID, pelvic inflammatory disease.

not address this issue because data about all conceptions are not routinely available, but live birth denominators have been accepted previously.[8 21] Finally, being an ecological study, we cannot make causal inferences about factors that might influence rates over time. We show yearly age-adjusted rates, and our area measures allowed comparisons between more or less affluent or urban and non-urban areas.

Comparison with other studies

We found admission rates in 2009 per 100 000 of 61 for PID and 110 for EP among women of reproductive age. An earlier Australian study (2001–2008) reported annual infertility admission rates for same-aged women of around 400 per 100 000.[22] Our overall PID admission rates were similar between 2009 and 2014, which is broadly consistent with a commissioned review presenting hospital discharge rates for inflammatory diseases of female pelvic organs (including any-cause PID) during 1990–2014 across Europe, America and Australia, showing declining country-specific rates to around 2007, which then appeared to plateau in several countries including Australia.[23] This is the first Australian study to assess PID rates using routinely collected ED data. Our findings of increasing PID rates contrast with a study in the USA that found falling PID rates (2002–2009) among adolescents attending EDs.[14] For EP, stable or declining admission rates using live birth denominators have been reported in Australia and internationally until the 2000s, with increases in some groups.[7 8 21] We found EP admission rates among live births in 2014 were 8% higher than for 2009. We are unaware of other studies measuring EP trends in EDs.

Interpretation of the findings

This study provides some evidence that declines in PID observed in Australia[7 8] and elsewhere[8] might have ceased or even reversed. Several factors might contribute to this. First, STI epidemiology and sexual behaviour might be changing, and PID is most common among young sexually active women.[2] Population-based data show increasing numbers of lifetime sex partners for young Australians, potentially increasing STI risk,[24] and surveillance data show increasing chlamydia and gonorrhoea rates among women that appear to reflect increased testing and transmission.[15] Other Australian data show higher risks for PID hospitalisation following gonorrhoea or chlamydia compared with no infection.[25] Although we found increasing CT-related PID rates and to a lesser extent NG, this might reflect increased testing or that clinicians are more likely to diagnose PID for women with lower abdominal symptoms and a positive test. Second, increased screening and treatment of diagnosed infections renders more women susceptible to reinfection. Chlamydia reinfection substantially increases PID risk[1 2 23] and is common; a repeat chlamydia diagnosis rate of 22% in the year after treatment has been reported in Australia.[26] Third, most PID cases were unspecified so other causes should be considered. *Mycoplasma genitalium* has been detected in 2.4% of Australian women attending primary care[27] and is receiving attention worldwide as a PID pathogen with worrying levels of antimicrobial resistance.[2 23] Bacterial vaginosis (BV) has been diagnosed in up to 12% of Australian women, and BV-associated microbes are often found in the upper genital tract of women with PID.[2 23] PID can also develop after uterine instrumentation, although this risk is greatest if an STI is present.[28] The extent these factors contribute to our findings is unknown and further research about PID causes is needed.

Australian data for 1998–2003 have shown around 59 000 PID general practice encounters annually.[20] Factors restricting primary care access could also contribute to increased ED rates. Timely access to Australian general practice is a concern particularly in non-metropolitan areas where there are ongoing workforce shortages,[29] which could contribute to higher STI rates,[15] thereby increasing PID risk. Further, out-of-pocket expenses[30] in primary care might prompt women to attend EDs instead for mild-moderate PID not requiring hospital admission. During the study period, the average out-of-pocket costs increased by 41%.[31]

Increasing EP rates could reflect increased risk of extrauterine conception or increased detection of extrauterine pregnancy. Risk factors for extrauterine conception include smoking,

postinfection tubal damage (particularly chlamydia), assisted reproductive technologies and older maternal age.[32] The extent these risks impact on EP rates is unknown, although smoking rates in pregnancy have declined and maternal age has increased in Australia, where EP-related mortality is rare.[33 34] Factors that increase EP diagnosis include more sensitive β-HCG tests to detect EP that might previously have resulted in undiagnosed tubal abortion, high-resolution transvaginal ultrasound, early pregnancy units and close monitoring of assisted reproduction outcomes. Our finding that a fifth of EPs in EDs were managed without admission is consistent with increased use of non-surgical (methotrexate) or conservative (wait and see) management[34] in some areas.

Implications for research, practice and policy

Prevention of PID and its associated complications is a key goal of STI control, yet trends in these conditions are generally not routinely monitored. The challenges in measuring PID and EP rates in this and other studies highlight the need for improved data sources and surveillance systems (reflecting hospital and primary care) that facilitate comparable measures over time. Australian policy identifies the need for interventions in primary care to enhance STI management, particularly partner notification and retesting.[4 23] Further analyses of hospital and primary care data can support evaluation of enhanced STI management impacts. Research is also needed to better understand the role of other infections in PID and to develop non-invasive and objective methods that can improve PID diagnosis in any setting.

In conclusion, we found increasing rates of PID and EP diagnosis in ED and EP hospital admissions. These results could represent changing sexual practices, increasing STI transmissions and reinfections, changing healthcare usage or increased EP detection from improved diagnosis. Without primary care data knowledge of PID epidemiology and healthcare use in Australia is incomplete. PID and EP remain important causes of hospital admission for STI-associated complications. EDs provide care for many additional PID cases, particularly for young women, warranting a strengthened focus on understanding the drivers of these rates and on reducing the risks of these sequelae.

Key messages

- Pelvic inflammatory disease (PID) and ectopic pregnancy remain important causes of hospital admissions for STI-associated complications among women of reproductive age.
- Emergency departments (EDs) care for many more PID cases, particularly for young women.
- PID rates in EDs were substantially higher for younger than older women.
- PID hospital admission rates varied little by age.
- Updated primary care data are needed to better understand PID epidemiology and healthcare usage, particularly given different patterns between hospital admissions and ED attendances.

Correction notice This paper has been amended since it was published Online First. The authors have noticed that in table 3 one line of results is missing for the year 2013. The table has since been updated to include this data.

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6.2 Chapter summary

This publication identified that rates of PID diagnosis in hospital admissions across three states (NSW, Victoria and Queensland) were similar between 2009 and 2014, which is in contrast with earlier downward trends observed in Australia and many other countries.[24] Investigation by PID category, showed that between 2009 and 2014 that admission rates increased by 73% for chlamydia or gonorrhoeal related PID, by 9% for unspecified PID, and, declined by 17% for chronic PID. Although overall PID admission rates varied little by age, chlamydial/gonorrhoeal PID rates were 11.7 times higher among women aged 15-24 than for women aged 35-44 years. Inclusion of emergency department data provided new information about PID diagnosis in Australia. The publication identified that emergency departments care for many more PID cases in addition to those managed as inpatients, that PID rates in emergency departments increased by 34% between 2009 and 2014, and, were substantially higher for younger than older women. The ectopic pregnancy analysis showed higher rates among live births in 2014 compared with 2009 in admissions and emergency departments. Although most ectopic pregnancy cases were admitted to hospital, an increasing proportion were managed without admission. Increasing disadvantage and remoteness of residential area tended to be associated with higher PID and ectopic pregnancy rates.

Interpretation of these findings is not straightforward. For PID, admissions data tell us largely about severe PID. However most PID cases are mild to moderate in severity and can be managed in primary care. Hence primary care data are need for a more comprehensive picture of PID. Increasing PID rates in the emergency department could suggest an increase in PID incidence but could also reflect changing healthcare usage. Over two thirds of women diagnosed with PID in the emergency department were managed without admission. It is possible that some of these women may have been suitable for management in primary care but that factors restricting access to primary care influenced them to attend the emergency department instead.[275 276] The higher PID rates observed among younger women, in particular STI associated PID admissions, and, PID in the emergency department, are consistent with higher chlamydia and gonorrhoea notification rates in this age group.[34] Rates of chronic PID were higher for older women which is consistent with other studies.[14] The decline in chronic

PID admission rates could reflect earlier declines in acute PID, that led to a smaller pool of women at risk of chronic PID. The challenges in measuring PID and EP rates in this study highlight the need for improved data sources and surveillance that include hospital and primary care to facilitate comparable measures over time. Considering systems for monitoring PID incidence are limited, this Chapter shows how ecological analyses of data from health settings where women with PID are managed can be used to measure PID trends.

Chapter 7: Discussion and Conclusions

7.1 Introduction

As outlined throughout this thesis, PID is a serious reproductive health issue for women that occurs when infection ascends from the lower to the upper genital tract. The STIs, chlamydia and gonorrhoea are commonly implicated, however the microbial aetiology of many cases is unknown. PID diagnosis is imprecise due to the wide range of possible clinical features and absence of an objective and reliable non-invasive diagnostic test.

In view of the potential long-term consequences of PID, it is essential that we have up to date knowledge about the number and distribution of PID cases within populations and the associated risk factors, to inform and assess progress against STI policies and programs. However, measuring the distribution and determinants for PID is challenging due to the issues around diagnosis, the many clinical settings where women with PID might be managed, and a scarcity of systems for routinely monitoring PID trends.

This PhD aimed to improve understanding of the epidemiology of PID diagnosed in Australia, particularly with reference to chlamydia infection. The thesis comprised four major components. Two separate quantitative analyses of routinely collected sexual health clinic data were undertaken to assess the microbial organisms associated with PID diagnosed in Australia. A third analysis of sexual clinic data investigated PID diagnosis characteristics and trends before and after clinical audit feedback. The final component was a quantitative analysis of routinely collected hospital data to assess yearly PID and ectopic pregnancy diagnosis rates for the period 2009 to 2014.

7.2 Objective 1 – To investigate the microbial organisms associated with PID diagnosed in Australian sexual health clinic attendees

7.2.1 Population attributable fraction of PID associated with chlamydia and gonorrhoea

The first component of this thesis sought to estimate the potentially avoidable burden of PID if chlamydia or gonorrhoea were eliminated from the population. The findings for the population level and individual level risks associated between PID and a current chlamydia or

gonorrhoea infection in female sexual health clinic attendees were published in *Sexually Transmitted Infections*[268] and are reproduced in full in Chapter 3.

A key finding in this publication was that for a high chlamydia prevalence clinic population, eliminating a current chlamydia infection might at most reduce PID by 14%. This was lower than an estimate of 19.7% derived from modelling of prospective, retrospective and routine data (see also Section 2.2.1). These modelled estimates were adjusted for under-ascertainment of chlamydia in PID cases in the retrospective studies, thereby increasing the PAF from 14.5%.[109] For a subset of women also tested for gonorrhoea the PAF of PID for gonorrhoea was 1%. A further sub-analysis for asymptomatic women showed that 28% of PID was associated with chlamydia but only 0.6% of asymptomatic women were diagnosed with PID.

These PAF findings provide valuable information in the context of ongoing debate as to whether chlamydia screening is an effective intervention. A systematic review of chlamydia screening trials found that PID risk was 32% lower in women who were offered a single chlamydia test compared with women not invited to have a test, although this effect was less when lower quality studies were omitted.[262] However the 32% reduction was similar to that observed recently in the ACCEPt study (also see Section 2.7.1, p 58) where a reduction of 40% in PID hospitalisations over a 3 year period was observed.[256] Even though there are some methodological issues with the trials, the consistency of their results does provide evidence for the protective impact of screening on PID. However, a cost analysis of one of the trials included in the systematic review, the POPI trial, estimated that the costs of chlamydia screening for women aged 16-24 years and living in London during 2009 were around £4 million to prevent around 400 cases of PID that incurred £64,000 in total of healthcare costs, leading to questions about the cost-effectiveness of screening.[263] While there is likely to be an individual benefit for those screened, there is unlikely to be sufficient population benefit to make it cost-effective.[256] For gonorrhoea, the population level findings suggest that gonorrhoea elimination in a sexual health clinic population would prevent a much smaller proportion of PID than chlamydia elimination, most likely reflecting that gonorrhoea is less common among Australian women compared with chlamydia infection.[35] Although in

consideration that gonorrhoeal PID can be more clinically severe than chlamydial PID, many gonorrhoeal PID cases may be represented in hospital rather than sexual health clinic data.

If Australia were to implement an organised chlamydia screening programme, the main setting would be general practice, where over 80% of young 16 to 29-year-old men and women attend at least once each year for their primary healthcare,[232] and, over 80% of Australia's chlamydia testing and diagnosis takes place. Given women attending Australian general practice are be more likely to be asymptomatic[277] than women attending a sexual health clinic, the PAF of PID in asymptomatic women provides an indication of how much PID might be avoided by chlamydia screening in general practice. As noted above, the PID prevalence for asymptomatic women was 0.6% (equating to 6 cases per 1000 patients) and with a PAF of 28%, chlamydia elimination might only avoid 1.7 PID cases per 1000 patients. If considered in the context of the UK cost analysis[263] and the ACCEPt study[256] it is likely to involve considerable costs to prevent these PID cases. In view of these population level findings, concerns about cost effectiveness of chlamydia screening (Section 2.7.1), and high rates of reinfection,[265] the emphasis of many discussions about chlamydia and STI control is shifting to a focus on primary prevention and strengthened case management. Optimising partner management to prevent reinfection and retesting to detect and treat repeat infections earlier are central to this debate.[23 115 248]

Although the population findings suggest that widespread screening may not be cost effective, the individual level findings showed a 4.4-fold and 3-fold higher odds of a PID diagnosis for women testing positive for gonorrhoea or chlamydia respectively than for woman testing negative. These individual level findings are consistent with other Australian data showing a higher risk of PID hospitalisation after a recent gonorrhoea or chlamydia diagnosis compared with no infection (Section 2.5.2).[40 41] In view of continuing high rates of chlamydia diagnosis and recent increases in gonorrhoea diagnosis rates for Australian women,[34] a continued focus on gonorrhoea and chlamydia case detection and PID diagnosis for women at STI risk or presenting with pelvic pain is essential. This information is also helpful for clinicians when managing women with a chlamydia or gonorrhoea infection, such as informing patients about the risk of PID and what to do should PID symptoms develop and in acting as a reminder to assess for presence of symptoms suggestive of PID.

7.2.2 Characteristics of pathogen negative PID

The study in Chapter 3 also found that 61% of PID cases did not have an infection identified, leading to a separate analysis of sexual health clinic data investigating the characteristics associated with PID without an identified pathogen (pathogen-negative PID). The findings for this analysis were published in *Sexually Transmitted Infections*[269] and are reproduced in full in Chapter 4.

This study found that of 330 women with clinically diagnosed PID who were tested for chlamydia, gonorrhoea, *M. genitalium* and *bacterial vaginosis*, that 62% tested negative for the four infections. This finding is consistent with other studies reporting that no pathogen was identified in a large proportion of PID cases.[18 19 140] However, the characteristics of PID without a pathogen have been infrequently reported. In this study women with clinical evidence of PID but no pathogen were more likely to be aged ≥30 years and less likely to have evidence of vaginal inflammation or to report recent unprotected sex than women with chlamydia, gonorrhoea, *M. genitalium* and/or bacterial vaginosis associated PID.

The study findings illustrate uncertainties about PID diagnosis and aetiology. Without well validated, objective and non-invasive diagnostic methods for PID diagnosis, the decision to initiate treatment for mild to moderate PID is reliant on sensitive minimum clinical criteria that aim to lessen the number of PID cases that are missed.[13] The study highlights the need for clinicians to weigh up the potential consequences of under-diagnosis of PID that could result in future adverse reproductive impacts[270] versus over-diagnosis of PID that may expose women to unnecessary antibiotic treatment. Side effects requiring discontinuation of PID treatment are infrequently reported,[213] however consideration of the potential for antimicrobial resistance, particularly for gonorrhoea and *M. genitalium* is important.[216] Although the study found that pathogen negative PID cases were at lower sexual risk than pathogen positive PID, the overall study population was high risk when compared to a national sample.[271] Sexual risk is an important factor for clinicians when considering differential diagnoses for a woman with new onset low abdominal pain.

The main characteristic differentiating women with pathogen-negative and pathogen-positive-PID was reduced evidence of vaginal inflammation. CDC guidelines note additional

clinical features that if present alongside the minimum clinical criteria can enhance PID diagnostic specificity. These include presence of one or more of elevated temperature, cervical friability or mucopurulent discharge, elevated erythrocyte sedimentation rate or C-reactive protein, abundant vaginal leukocytes, and a lower genital tract chlamydia or gonorrhoea infection.[13] However, requiring all features to be present comes at the expense of diagnostic sensitivity and would reduce the number of cases identified.[13 16 201-203] Several studies have assessed indicators of lower genital tract inflammation on their own or in combination with other criteria for their use in supporting a PID diagnosis. The presence of mucopus or white blood cells in vaginal discharge from a sample of women enrolled in the PEACH study was found to have high sensitivity (88.9%) but low specificity (19.4%) for upper genital tract infection as confirmed by endometrial biopsy.[203] However, a 2009 review that included the PEACH [203] and 12 other studies, concluded that for women with clinical evidence of PID, the presence or absence of vaginal or cervical discharge was not helpful in making or excluding a PID diagnosis.[272] Another analysis from the PEACH study assessed combinations of clinical features for supporting a PID diagnosis. In women with adnexal tenderness and an abnormal cervical-vaginal discharge, the probability of endometritis was only above 65% if the woman also had a positive chlamydia or gonorrhoea test result, or, if the woman also had an elevated temperature and an elevated leukocyte count.[201] For the publication presented in Chapter 4, it is possible that some pathogen negative PID cases, particularly if evidence of vaginal inflammation was absent, were false positive diagnoses for which the woman did not have PID or an STI.

The microbial causes of PID are difficult to determine. It is possible that some pathogen-negative PID cases were associated with an STI that had cleared from the cervix but had ascended to the upper genital tract[96] or with other bacteria, viruses or other micro-organisms that were not identified.[99] Respiratory, enteric or novel bacteria and bacterial vaginosis associated pathogens have been identified in the upper genital tract of women with non-gonococcal or non-chlamydial PID, although some of these pathogens have also been present in women without PID.[2 96-99] PID is strongly associated with bacterial vaginosis. Several studies have assessed specific bacterial vaginosis associated pathogens, reporting that women with high levels of Gram negative anaerobes in the lower genital tract are at higher risk of PID.[97]

[166] [177] Women with bacterial vaginosis are also at higher risk of incident chlamydia or gonorrhoea infection[180] that could in turn increase their risk of ascending infection.

Antimicrobial therapy for PID aims to cover the likely pathogens. The publication in Chapter 4 provides evidence about the frequency of pathogens in a sample of Australian PID cases and this is information that has been infrequently reported. Among the 330 PID cases, bacterial vaginosis was the most frequently diagnosed infection (21.5%), followed by chlamydia (18.8%), *M. genitalium* (4.5%) and gonorrhoea (2.4%). Of 25 PID cases with more than one infection diagnosed, all but two were coinfected with bacterial vaginosis. Australian guidelines for PID management in primary care (Section 2.4.2) recommend cover for chlamydia, gonorrhoea and anaerobes as first line treatment with the addition of moxifloxacin if *M. genitalium* is diagnosed.[216]

7.2.3 Summary

In summary, the studies toward objective 1 provide updated evidence for the frequency of PID pathogens in Australia and new information based on the PAF. Importantly, the PAF findings suggest that for a high chlamydia prevalence population that eliminating chlamydia might only reduce PID by 14%, and, that in a low chlamydia prevalence population that widespread chlamydia screening might only prevent a small number of PID cases. The population level findings also suggest that chlamydia elimination might prevent a greater proportion of PID than gonorrhoea. At individual level, women with a gonorrhoea or chlamydia diagnosis were over three times more likely to be diagnosed with PID than women with no infection. The pathogen-negative PID findings highlight uncertainties around PID diagnosis and aetiology and the need for biomarkers of upper genital tract inflammation that can improve certainty of a PID diagnosis.

7.3 Objective 2 – To investigate time trends in PID diagnosis in an Australian sexual health clinic

The third component of this thesis investigated PID diagnosis characteristics and time trends in a sexual health clinic, before and after clinical audit feedback. The challenges in clinically diagnosing PID are well known. As noted in Chapter 5, an Australian sexual health clinic implemented actions toward improving consistency of PID diagnosis after a clinical audit

identified variability in PID diagnosis rates between doctors. It was unknown whether PID diagnosis rates had altered following the audit response, leading to the analysis in Chapter 5. A manuscript of the findings is currently under review by the journal *Sexual Health* and is reproduced in full in Chapter 5.

This was the first study to examine PID diagnosis time trends in an Australian sexual health clinic, showing that over a 14-year period the yearly PID diagnosis rate increased substantially from 0.8% to 2.9%. In the nine-year period following audit feedback the PID diagnosis rate increased by 8% yearly. However, after accounting for patient characteristics in the multivariable analysis this increase was no longer evident. As noted in Chapter 5, this finding appears to be influenced by substantial changes in the risk profile of patients assessed by doctors in the clinic and highlights the importance of adjustment for patient characteristics in interpreting time trends.

Occurring around a decade ago, the PID focussed strategies in response to the audit included benchmarking and self-appraisal by doctors of their diagnostic criteria about whether they could be more sensitive to a PID diagnosis. Anecdotally some doctors considered these activities helped them to appraise their diagnostic criteria. The finding of less deviation in doctor-specific rates from overall PID rates after audit feedback suggests some change in clinical practice, although whether because of the audit is not known. There is a risk that an emphasis on diagnostic sensitivity could compromise specificity, potentially delaying care for another condition. Although the difficulties in PID diagnosis have led to assessments of the clinical criteria that best correlate with upper genital tract infection[201 278] the minimum criteria of any one of cervical motion, uterine tenderness or adnexal tenderness as outlined in CDC guidelines remain the mainstay of PID diagnosis[13] and further highlight the need for a simple non-invasive test that can accurately diagnose PID.

Melbourne Sexual Health Centre is the only full-time and free sexual health service in the Australian state of Victoria and in response to increasing demand has implemented changes toward improving clinical efficiency. As noted in Chapter 5, one internal change was implementation of a nurse express testing service[273] that streamlined care for asymptomatic patients and increased capacity for more high risk symptomatic patients in the clinic. Externally, change to the required interval for screening sex-workers from three monthly[279]

also contributed to increased clinic capacity.[280] In this context, doctors in this study undertook an increasing number of female consultations, including for high risk women and diagnosed many additional PID cases.

The findings in Chapter 5 have implications for PID diagnosis in other clinical settings (such as general practice) that provide care for women with PID[21 110] but where sexual health care is not core business. Strategies toward improving PID diagnosis and management (see section 2.4.3) have had only moderate success and the evidence base largely comes from hospital settings in the USA.[46 47 222 223] For Australia, resources such as the PID checklist (described in Chapter 5) or an algorithm for assessing abdominal pain in women[199] could be applicable to the general practice setting. However, the challenge is to systematise such resources into routine care, and, to provide education and training to support their uptake.

In summary, it was uncertain whether PID specific actions after a clinical audit led to changes in PID diagnostic sensitivity. Service improvements appeared to have had a greater impact on PID trends, providing additional capacity for high-risk patients and an increase in the overall number of PID cases diagnosed and managed.

7.4 Objective 3 – To estimate time trends in PID diagnosis in Australian hospitals

The final component of this thesis investigated yearly rates of PID diagnosis in Australian hospitals, the findings were published in *Sexually Transmitted Infections*[274] and are reproduced in full in Chapter 6. Although PID is the outcome of focus in this thesis, ectopic pregnancy rates were investigated in this publication as another measure of female reproductive tract morbidity.

This study reported that in contrast to reported declines or static hospital admission rates of PID and ectopic pregnancy in Australia to around 2007[24] that rates between 2009 and 2014 were no longer declining and increased in some instances. For example, admissions rates of chlamydial and to a lesser extent gonorrhoeal PID increased by 73%, unspecified PID by 9%, while chronic PID rates declined by 16%. PID rates in emergency departments increased by 34%. Hospital admission and emergency department rates of PID showed a very different age-related pattern. Overall PID hospital admission rates varied little by age, whereas emergency department rates were substantially higher for younger than older women. Most

PID cases were unspecified, for which the causes are unknown. Most STI-associated PID admissions were among younger women and most chronic PID admissions were among older women, which is consistent with other studies.[14]. Areas of residence that had greater socio-economic disadvantage and were more remote also experienced higher PID rates. The ectopic pregnancy analysis showed higher rates among live births in 2009 compared with 2014 in admissions and emergency departments. Although most ectopic pregnancy cases were admitted to hospital, an increasing proportion were managed without admission, consistent with increased use of non-surgical management for ectopic pregnancy in some areas.[281]

As noted in Chapter 6, interpretation of these findings is not straightforward. These results could represent changing sexual practices, increasing STI transmission and reinfections, changing healthcare usage or increased EP detection from improved diagnosis. The increasing admission rates for chlamydial, gonorrhoeal and unspecified PID and increasing PID rates in the emergency department could reflect a complex interplay of factors. Case detection is an important component of Australian STI policy[21] and surveillance data have shown recent increases in chlamydia and gonorrhoea rates for Australian women that have been attributed to increased testing and transmission.[34 35] The increases in chlamydial and gonorrhoeal PID admissions could reflect increased testing or increasing awareness of PID as a provisional diagnosis for women with lower abdominal pain and a positive STI test. Furthermore, in a context of increased testing and treatment of diagnosed infections, more women will be at subsequent risk of reinfection. As discussed earlier (Sections 2.2.1, 2.3, 2.7.1), chlamydia reinfection increases a woman's risk of PID[115] and high reinfection rates in Australia have been reported.[265] Other factors associated with PID include *M. genitalium,* bacterial vaginosis and procedures involving uterine instrumentation,[27 115] although the extent they have contributed to these findings is unknown. It is unclear whether the admissions coded as chronic PID were for chronic pelvic pain as sequelae of PID or another chronic pelvic inflammatory condition. Most chronic pelvic inflammatory conditions were coded as chronic salpingitis or oophoritis, suggesting they were sequelae of an earlier infection. The decline in chronic PID admissions could reflect earlier declines in acute PID[14 24] that led to a smaller pool of women at risk of chronic PID.

The increasing rates of PID diagnosis in emergency departments are a cause for concern, particularly given that over two-thirds were managed without admission. Australian guidelines recommend out-patient management for mild to moderate PID,[200] that includes general practice. The reasons these women attended an emergency department are not known, but it is possible that many were suitable for management in general practice. Work-force shortages particularly in non-metropolitan areas,[275] and out-of-pocket expenses incurred when attending general practice [232 276] could adversely impact on a woman's ability to access general practice for timely and affordable sexual health care, thereby placing them at increased risk of an STI ascending to the upper genital tract, and, influencing them to attend the emergency department for mild to moderate PID instead. These findings could also reflect inadequacies in PID diagnosis and management[48 217] and STI care in general practice.

Recent STI policy in Australia, has had a strong focus on testing coverage. The PID and ectopic pregnancy rates presented in this study provide valuable information about the epidemiology and healthcare usage for these conditions, showing that PID and ectopic pregnancy remain important causes of hospital admission for STI-associated complications among women of reproductive age. Inclusion of emergency department data provided new information about PID diagnosis in Australia showing that emergency departments provide care for many additional PID cases, particularly for young women, warranting a strengthened focus on reducing the risks of these sequelae. However primary care data are needed for a more complete picture of PID epidemiology and healthcare use, particularly given different patterns between hospital admissions and emergency department attendances.

There is no ongoing mechanism for monitoring PID incidence in Australia. The challenges in measuring PID and ectopic pregnancy rates in this ecological analysis of routinely collected data highlight the need for improved data sources and surveillance that include hospital and primary care data to facilitate comparable measures over time. Data linkage has been used to quantify the risk of a PID hospitalisation following a chlamydia or gonorrhoea diagnosis[41] and could facilitate measurement of the temporal relationship between STIs and complications, including the risk of PID following repeat infection. In view of unchanging chlamydia prevalence despite increases in testing[115 254] and high rates of chlamydia reinfection,[22 192] improving case management has been a focus of recent debate about

chlamydia and STI control.[115] In particular the need for methods to improve partner notification to reduce onward transmission and reinfections, and, retesting to detect repeat infections early are identified. The impact of such measures on PID should also be monitored.

In summary, the study toward objective 3 showed that PID remains a substantial reproductive health issue for young women in Australia and an important burden on the healthcare system. While overall hospital admission rates remained steady between 2009 and 2014, the analysis of hospital data found that chlamydial or gonorrhoeal PID comprised a small but increasing proportion of PID admissions and chronic PID rates declined. PID rates were consistently higher for younger women suggesting an STI aetiology even if an STI was not confirmed. Areas of residence that had greater socio-economic disadvantage and were more remote also experienced higher PID rates. Considering systems for monitoring PID incidence are limited, this study shows how ecological analyses of data from health settings where women with PID are managed can be used to measure PID trends.

7.5 Challenges

There remain several challenges with understanding diagnosis and managing PID. Broadly these challenges can be viewed as relating to PID aetiology and diagnosis, issues related to availability of data to investigate PID epidemiology, and analytical challenges.

7.5.1 Challenges posed by PID aetiology and diagnosis

First and foremost, is that clinical diagnosis of PID is imprecise and there is no non-invasive and objective test for its diagnosis. Therefore, for studies involving PID as an outcome, there is uncertainty about the precision of estimated trends and associations.[4 22 205] Related to this is that the natural history of many STIs and their relationship to PID and more distant outcomes is not fully understood. While prevention of infertility or other outcomes such as ectopic pregnancy is an important rationale for STI control policies,[21 22] PID is often used as an interim measure of STI morbidity because the timeframes to sequelae such as infertility are longer and may not be recognised until affected women try to conceive. Despite these challenges, epidemiological and ecological studies analysing routinely collected data provide much of the knowledge about PID incidence and its relationship with STIs. As in this Thesis, it is important that they are robustly conducted but cautiously interpreted to provide current

and updated information about PID and STIs. This issue reinforces the need for objective non-invasive diagnostic biomarkers for PID that can not only improve precision of PID diagnosis to benefit individual patients but will improve precision of clinical and epidemiological studies assessing PID.

7.5.2 Challenges posed by routinely collected data sources for data measuring PID

A second challenge was the availability and usefulness of routinely collected data to answer questions about PID. This thesis analysed data from two routinely collected sources, each with strengths and limitations for answering questions about PID.

Sexual health clinics in Australia are a key primary care setting for patients at high sexual risk to access specialist care. Data were obtained from Melbourne Sexual Health Centre, the state of Victoria's only free full time sexual health service servicing a state population of over 6 million. The clinic has a well-established electronic clinical record system that collects demographic and risk behaviour data from all new patients then at three-monthly intervals for repeated visits. This electronic record also collects clinical data (STI tests, diagnoses) that are easily extracted (and deidentified as required) for epidemiological analyses such as investigating the microbial associations of PID. However, for female non-sex worker patients, repeat visits are generally limited to four weeks after the first visit. This meant it was not possible to assess long-term temporal relationships between STIs and sequelae for individual women. To maximise data completeness, cross-sectional analyses of a woman's first episode of care were conducted. This provided a large sample size with complete case data for over 15000 women. Another limitation of these sexual clinic data was how the variable classifying women as symptomatic or asymptomatic was derived. As noted in the three studies analysing these data, clinic attendees are asked to report any presenting symptoms at triage. It is possible that some female patients who did not report symptoms at triage, subsequently reported symptoms suggestive of PID to the clinician during the history taking and clinical examination. If this occurred, there would be some inaccuracy in the symptoms at triage variable, in which some women that later reported symptoms were classified as asymptomatic.

In Australia, hospital admission data systems are managed at a State level and collect data for all hospitalisations at public and private hospitals with diagnoses codes based on International Classification of Diseases (ICD-10) codes[282] assigned by trained coders. Emergency department data systems are also managed at State level and collect data about presentations to public hospitals with a designated emergency department[237] Data reporting from emergency departments is voluntary, and diagnosis codes are assigned by clinicians, making emergency department data more variable than admissions data. Diagnosis codes in emergency departments were based on ICD10, ICD9 or Systematized Nomenclature of Medicine (SNOMED) codes.[283] Due to these differences in data systems there were many challenges in constructing a dataset for analyses of PID and ectopic pregnancy rates. Approvals were required from State departments of health in Victoria, NSW and Queensland before data from six separate data systems could be extracted, validated, and re-extracted (if indicated). Extensive formatting and cleaning was involved to combine these data into a separate dataset for hospital admissions and emergency department presentations. Because the analysis focussed on trends, emergency department data were only included if they arose from hospitals that contributed data for the entire study period and if there was low variability in the annual number of presentations. These challenges in constructing a dataset for investigation of PID diagnosis trends, again highlights the need for improved data sources and surveillance that facilitates comparable measures over time.

7.5.3 Analytical challenges

The main analytical challenges in this research is related to missing data, and, that at residential postcode level, PID can be a relatively infrequent outcome.

In the sexual health clinic dataset for investigation of the PAF of PID associated with chlamydia or gonorrhoea there were 18,586 women eligible for the study. Complete case data were available for 15690 chlamydia tested women, and, a subset who were also tested for gonorrhoea (n=8839). To assess the impact of missing data a sensitivity analysis using multiple imputation was conducted, and the odds ratios from the univariable and multivariable logistic regression models for the complete case analysis were compared with those derived from the multiple imputation models. A description of the two imputation models and their results were published as supplementary information to the publication in

Chapter 3. The estimated adjusted odds ratios for PID from the complete case analysis for chlamydia-tested women, chlamydia + gonorrhoea-tested women and multiple imputation were very similar in this analysis.

In the hospital dataset for assessment of yearly rates of PID, the admissions and emergency department data were analysed at the level of residential postcode using population denominators. Across 1678 postcodes in three states, around one fifth had no PID cases recorded in the hospital admission or emergency department data. In consideration that there were large numbers of postcodes with no cases, zero inflated Poisson regression was used to assess variation in yearly rates. The fit of the zero-inflated Poisson models was compared to ordinary Poisson models using the Vuong test.

7.6 Ethical considerations

The main ethical considerations in this PhD are related to privacy, sensitive information related to STIs and PID, and age. Privacy of individual patients was protected as follows: no direct contact was made with any patient; all patient data came from secondary sources and reflects routine clinical care; all data files were stored on password protected secure servers; and all reporting was at aggregate level so that no sensitive information was potentially identifiable to any one individual. All studies only considered patients aged 15 years or over.

7.7 Implications for practice, policy, and research

This thesis has sought to provide updated evidence about the epidemiology of PID diagnosed in Australia, particularly with reference to chlamydia infection. Based on quantitative analyses of routinely collected sexual health clinic and hospital data, I have investigated the risk of PID associated with chlamydia and gonorrhoea infection; the microbial characteristics of PID cases including pathogen negative PID; PID diagnosis characteristics and trends in a sexual health clinic; and how much PID is diagnosed in Australian hospitals over time. The findings have implications for clinical practice, STI control policies, and future research.

7.7.1 Implications for clinical practice

Chlamydia and gonorrhoea are well established PID pathogens (Section 2.2). The study in Chapter 3 found that the risk of a PID diagnosis was 4.4-fold and 3-fold higher for women

testing positive for gonorrhoea or chlamydia respectively than for woman testing negative for these infections. This information can inform the clinical discussion and assessment. Women diagnosed with chlamydia or gonorrhoea should be advised that these infections can cause PID and that they should return for review should symptoms such as pelvic pain or dyspareunia develop. This advice also applies for women diagnosed with *M. genitalium* infection. This knowledge of individual PID risk could also remind clinicians when prescribing STI treatment to assess for presence of symptoms such as pelvic pain, abnormal discharge or dyspareunia that suggest PID. In addition, PID should be considered as a differential diagnosis for any young women at STI risk and presenting with low abdominal pain.

The study in Chapter 4 found that chlamydia or bacterial vaginosis were the most commonly identified infections in women with clinically diagnosed PID, followed by *M. genitalium*, and gonorrhoea. Australian guidelines are consistent with these findings, recommending antibiotic cover for chlamydia, gonorrhoea and anaerobes as first line treatment, with the addition of cover for *M. genitalium* if diagnosed.[216] Although chlamydial PID was more common that gonorrhoeal PID, recent increases in heterosexually transmitted gonorrhoea in Australia[34 35] could impact on the frequency of gonorrhoeal PID diagnosed in primary care and hospital settings. In Australia and internationally there is growing concern about the reduced susceptibility of gonorrhoea to ceftriaxone, so continuing surveillance is essential to inform treatment guidelines.[21 110]

The study in Chapter 4 illustrates the uncertainties about PID diagnosis and aetiology, finding that almost two thirds of PID cases had no pathogen identified. Although some of the pathogen-negative PID cases may have been false positives, this is consistent with minimum criteria that recommend a low threshold for a PID diagnosis.[13] The difficulties in diagnosing PID and the frequent lack of association with a causative organism further highlight the need for biomarkers of upper genital tract inflammation that can improve certainty of a PID diagnosis. Until we have well-validated rapid biomarkers that improve precision of clinical PID diagnosis, the basis for PID diagnosis and treatment should continue to be based on clinical features and sexual risk rather than microbiological findings.

7.7.2 Implications for STI control

STI control involves a range of primary and secondary prevention activities that seek to reduce the incidence of STIs and their associated morbidities, including PID and other adverse female reproductive impacts (Section 2.7).[21 139 248] Knowledge of the attribution of STIs to PID can provide policy makers with information about where to target control activities and their potential impact.

The PAF analysis in Chapter 3 provided a measure of how much PID might be avoided if chlamydia or gonorrhoea were eliminated from a population. The key finding was that for a high chlamydia prevalence clinic population, eliminating a current chlamydia infection might at most reduce PID by 14% whereas gonorrhoea elimination might only reduce PID by about 1% reflecting the low gonorrhoea prevalence in the study population. Although as noted earlier, recent increases in heterosexual transmission of gonorrhoea[35] could translate into a higher proportion of PID cases being gonorrhoeal associated.

Over the past two decades STI and chlamydia control actions in Australia and other high-income countries have had a strong focus on testing coverage to detect asymptomatic infections, with chlamydia screening debated as an intervention that might reduce transmission and complications.[21 257 258 284-286] If Australia were to implement an organised screening programme, the main setting would be general practice, being where most chlamydia testing and diagnosis occurs. Given that asymptomatic presentation maybe more common for women attending general practices than sexual health clinics, the study in Chapter 3 also reported the PAF of PID associated with chlamydia for asymptomatic women. The findings suggested that chlamydia elimination in a low prevalence setting might only prevent a small number of PID cases. If considered in the context of the ACCEPt study that found it was not possible to reduce chlamydia prevalence in the population with achievable levels of annual testing,[256] and a UK cost analysis that reported over £4 million in chlamydia screening costs to prevent around 400 PID cases,[263] the costs of PID prevention via chlamydia screening in general practice could be substantial (Section 2.7.1). Recent debate about chlamydia and STI control has seen some countries shift to an increased focus on improving case management to reduce the risk of reinfections and complications.[23 115 248]

An important finding reported in Chapter 6 was that PID diagnosis rates increased in hospital emergency departments between 2009 and 2014, and, that over two-thirds of PID in the emergency department was managed without admission. The reasons these women attended an emergency department are not known, but it is possible that many were suitable for management in general practice. This finding could reflect inequitable access to general practice for reasons such as out-of-pocket expenses[232] [276] or low availability of timely appointments[287] and inadequacies in STI and PID diagnosis and management in primary care.[48] [217] Other Australian evidence shows sub-optimal rates of partner notification and retesting after chlamydia treatment in general practice[264] that can increase the risk PID. There is a clear need for strengthening STI case management in the primary care sector that prioritises effective partner notification to prevent reinfection, timely re-testing after treatment to detect re-infection earlier and to reduce complications. The need for new or improved care models in primary care to enhance STI management and their complications is identified in Australian policy[21] and will be explored in a research project for implementing an integrated chlamydia management program in general practice.[288]

7.7.3 Measuring PID trends

Although this research has provided a measure of recent PID time trends in hospital, it is difficult to directly compare the findings to other standalone studies conducted in different countries, settings or time periods. The need to develop indicators for monitoring STI-related morbidity has been identified in Australian policy[21] and in international guidance regarding chlamydia control.[115] The Australian state of NSW has recently developed an indicator of chlamydia morbidity via data linkage of chlamydia notifications and PID hospital admissions for its STI strategy.[289] Although useful, this indicator only measures chlamydia associated PID cases that are severe enough to require hospital admission. The analysis of emergency department data[274] and other analyses [228] have shown that a large burden of PID is managed without admission.

Some other suggestions for monitoring PID are provided here. As noted earlier (Section 7.4), there is a need for improved data sources and surveillance that includes data from health settings that PID cases are managed (hospital admission, emergency departments, primary care) to facilitate comparable measures of PID over time. In view of recent increases in

gonorrhoea diagnoses among Australian women[34 35] and the increased risk of PID hospitalisation following a gonorrhoea infection,[41] consideration of gonorrhoea and chlamydia in indicators of PID is imperative. Such systems could involve data linkage to facilitate measurement of the temporal relationship between STIs and complications, and, to assess patterns in health care usage, for example rates of admissions from primary care or the emergency department. PID cases represented in hospital inpatient and emergency department data could be categorised using ICD10 codes to provide a measure of STI-associated PID, unspecified PID and chronic PID. An overall measure of PID incidence could be determined by the addition of non-admitted emergency department cases and cases managed in primary care to the number of cases in managed as inpatients, using population denominators. Alternatively, sentinel surveillance for PID could involve collection and analysis of data from selected emergency departments, hospitals, and primary care clinics (sexual health, women's health clinics, general practice).

7.7.4 Improving PID diagnosis

This PhD research has highlighted the need for an evidence base regarding resources and processes that can support improvements in PID diagnosis and management in the Australian context. The study of PID diagnosis trends in the sexual health clinic (Chapter 5) showed that service improvements created extra capacity for the number of high-risk patients and PID cases diagnosed, but it was uncertain whether PID specific actions after a clinical audit led to changes in PID diagnostic sensitivity. In addition, the study of PID rates in hospitals (Chapter 6) showed increasing PID rates in emergency departments that could reflect issues in access and/or inadequacies in PID diagnosis and management in general practice clinics. Given that general practice is Australia's mainstream primary care setting where many women with STIs or mild to moderate PID are likely to present, it is imperative this sector is resourced with the tools and activities to provide best practice STI and PID care.

Toward this objective, Australian policy identifies the need for innovative models of care that support timely and appropriate referral between primary healthcare and specialist services, and, that incorporate interventions shown to be effective in improving treatment and management.[21 250] Some examples of interventions that have been evaluated in specialist settings include partner notification websites[266] and promotion of retesting for STIs after an

earlier positive test via SMS reminders and mailed specimen kits.[267] However their feasibility and impact in the general practice setting is not known. For PID, the checklist developed by MSHC (Chapter 5) and a decision tree for assessment of low abdominal pain in women of reproductive age and possible differential diagnosis[199] were developed with an objective to support decision making for a PID diagnosis. Again, their impact in general practice is unknown. Assessment of the feasibility and impact of these resources toward improving PID diagnosis and management should be accompanied by workforce training and educational resources to integrate them into routine general practice care.

7.8 Conclusions

This thesis provided the first Australian estimates of the population level risk of PID associated with chlamydia and gonorrhoea. This new information based on the PAF suggests that eliminating chlamydia in a high prevalence population might only reduce PID by 14% and around 1% if gonorrhoea were eliminated, and, further for low chlamydia prevalence populations, that only a small number of PID cases might be avoided by widespread screening. Updated evidence was provided for the frequency of PID pathogens in Australia, and, the need for non-invasive bio-markers for upper genital tract inflammation was highlighted by the many cases without an identified pathogen. In the absence of bio-markers the decision to commence PID treatment should continue to be based on clinical features and sexual risk. This thesis found that PID remains a substantial cause of attendances at sexual health clinics and hospitalisations for reproductive related health issues for women in Australia. Analyses of sexual health clinic data demonstrated the importance of adjustment for patient characteristics in interpreting time trends, and, investigation of hospital data showed how ecological analyses of data from health settings where women with PID are managed can be used to measure PID trends. Evidence was provided for an increase in PID diagnosed in Australian emergency departments that could reflect increasing PID incidence, shifting healthcare usage from primary care, or, inadequacies in PID diagnosis and management in primary care. Primary care data and systems to monitor PID incidence are needed to better understand PID epidemiology, healthcare usage, and the impact of chlamydia and STI control policies.

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Appendices

Appendix 1 Supplementary online material for the publication in Chapter 3

Appendix 1 provides additional material that was published online only at http://dx.doi.org/10.1136/sextrans-2015-052195 with the publication that is reproduced in Chapter 3.

Sexually Transmitted Infections

Supplementary file 1: Population attributable fraction of pelvic inflammatory disease associated with chlamydia and gonorrhoea: a cross-sectional analysis of Australian sexual health clinic data

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Supplementary table 1: Characteristics of eligible women and women in the *chlamydia-tested* and *chlamydia+gonorrhoea tested* datasets

		Eligible women		Chlamydia-tested[a]		Chlamydia+gonorrhoea tested[b]	
		n	%	n	%	n	%
Total		18586		15690		8839	
Age group	16-29 years	14020	75.4	12080	77.0	6596	74.6
	30-49 years	4566	24.6	3610	23.0	2243	25.4
Australian born		7973	42.9	6529	41.6	3591	40.6
Any symptoms at presentation		8395	45.2	7342	46.8	5834	66.0
PID[c] diagnosed		465	2.5	436	2.8	419	4.7

a: Chlamydia-tested group is a subset of the 18586 eligible women, b: Chlamydia+gonorrhoea tested group is a subset of the chlamydia-tested group; c: PID – pelvic inflammatory disease

Sexually Transmitted Infections

Supplementary file 2: Population attributable fraction of pelvic inflammatory disease associated with chlamydia and gonorrhoea: a cross-sectional analysis of Australian sexual health clinic data

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Supplementary table 2: Predictors of PID[a] among *chlamydia tested* and *chlamydia+gonorrhoea tested* women following multiple imputation[b] of the following variables with missing data: chlamydia test, condom use with male partners in the past three months, gonorrhoea test.

		Chlamydia tested					**Chlamydia+Gonorrhoea tested**				
		Univariable		**Multivariable**			**Univariable**		**Multivariable**		
		OR	**95%CI**	**AOR**	**95%CI**	**p**	**OR**	**95%CI**	**AOR**	**95%CI**	**p**
Age group (years)	16-29	1.5	1.2-1.9	1.3	1.0-1.7	0.025	1.4	1.1-1.8	1.3	1.0-1.7	0.054
	30-49	1.0		1.0			1.0		1.0		
Country of birth	Australia	1.0	0.8-1.2				1.1	0.9-1.3			
	Other	1.0					1.0				
Current contraception	Any hormonal	1.0	0.8-1.3	0.9	0.7-1.1	0.249	1.0	0.8-1.3	0.9	0.7-1.1	0.229
	IUD	2.7	1.6-4.3	2.6	1.6-4.2	<0.001	2.6	1.6-4.3	2.5	1.5-4.2	<0.001
	Other/not reported	1.0		1.0			1.0		1.0		
Chlamydia test results	Negative	1.0		1.0			NA				
	Positive	3.5	2.7-4.3	3.2	2.5-4.0	<0.001	NA				
Chlamydia and gonorrhoea test results	Negative	NA		NA			1.0				
	Chlamydia positive only	NA		NA			3.2	2.5-4.1	3.0	2.3-3.8	<0.001
	Gonorrhoea positive only	NA		NA			4.5	1.6-12.1	4.0	1.5-10.9	0.007
	Chlamydia and gonorrhoea	NA		NA			6.8	2.5-18.4	5.9	2.2-15.9	<0.001
Condom use with male partners, last 3 months	No male partners/vaginal sex	0.2	0.1-0.4	0.2	0.1-0.4	<0.001	0.2	0.1-0.5	0.3	0.2-0.5	<0.001
	Always	0.5	0.4-0.7	0.5	0.4-0.7	<0.001	0.5	0.4-0.7	0.6	0.4-0.8	<0.001
	Not always	1.0		1.0			1.0		1.0		

a: PID - Pelvic inflammatory disease

b: Two imputation models were used to manage missing data:

1. The first considered all women eligible for the study (n=18586). Values were imputed for the following variables i) chlamydia test in 2016 women, and ii) condom use (past three months) for 1122 women including all the following variables: PID, age-group, born in Australia, and contraception in the imputation model to generate a total of 20 completed datasets. The decision to limit imputation of sexual behaviour data to condom use (past 3 months) was guided by the complete case analysis where this was the key sexual behaviour variable associated with PID.
2. The second considered all women in the chlamydia tested dataset (n=15690). Values were imputed for gonorrhoea test for 6851 women, using the variables chlamydia test, PID, age-group, born in Australia, and contraception in the imputation model to generate a total of 20 completed datasets.

Appendix 2 Supplementary online material for the publication in Chapter 6

Appendix 2 provides additional material that was published online only at http://dx.doi.org/10.1136/sextrans-2017-053423 with the publication that is reproduced in Chapter 6.

Rates of pelvic inflammatory disease and ectopic pregnancy in Australia, 2009 to 2014: ecological analysis of hospital data

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Supplementary online material. Supplementary material for Sex Transm Infect

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METHODS

A description of data sources and diagnosis codes used to identify primary diagnoses of pelvic inflammatory disease (PID) and ectopic pregnancy (EP) is provided in supplementary tables 1 and 2 and described below.

Data sources for hospital admissions and emergency department presentations of PID and EP

We obtained line-listed data about admissions to hospital and attendances at emergency departments (EDs) for 15 to 44 year old female patients with a principal diagnosis of PID or EP from separate registers from state Departments of Health in the Australian states of New South Wales, Victoria and Queensland.

Hospital admitted data systems collect data for day cases and overnight hospitalisations from all public (government funded) and private hospitals in the state. Diagnoses codes for episodes of patient care assigned are assigned by trained coders following discharge. In 2014, data systems about hospital admissions for the three states included data for 998 hospitals.[1 2]

ED information systems collect data about emergency presentations to public hospitals with a designated ED that include major metropolitan and non-metropolitan EDs and represented an estimated 88% of ED occasions of service in 2014.[3 4] Notably, the number of EDs included in ED information systems has increased over time, contribution of data by hospitals to ED systems is voluntary, and diagnosis codes are assigned by clinicians rather than medical record coders. Therefore, the number and breakdown of hospitals contributing data annually varies and data completeness varies between hospitals. In the three states, the number of hospitals contributing data about ED attendances increased from 151 (during July 2010 to June 2011) to 247 (during July 2013 to June 2014). The increase in the number of hospitals reporting ED attendance data during the study period was mostly due to an increase in reporting for small non-principal hospitals.[4] To maximise comparability over time, ED records were only included if they arose from EDs that annually contributed data during 2009-2014, if there was <50% variability in the annual number of presentations, and ≥75% records had a principal diagnosis coded. For this study, ED data were included for 145 hospitals (metropolitan n=75, inner-regional n=49, outer-regional/remote n=21).

Each patient record included a principal diagnosis for the main reason for admission or emergency presentation and 'other' diagnoses for additional diagnoses made coded using the International Classification of Diseases (ICD10-AM) or for some EDs, ICD9-CM or Systematized Nomenclature of Medicine (SNOMED).[4-6] The number of other diagnosis codes available varied between jurisdictions. We excluded records with an 'other' PID or EP diagnosis because they might represent pre-existing conditions. Admissions or ED presentations with a principal diagnosis ICD10-AM (or concordant ICD9-

CM or SNOMED) of: i) N70.0, N70.1, N70.9, N71.0, N71.1, N71.9, N73.0, N73.1, N73.2, N73.3, N73.4, N73.5, N73.8, N73.9, A56.1, N74.4, A54.2, N74.3, were classified as PID; or, ii) O00.1, O00.2, O00.8, O00.9 as EP. PID admissions were further categorised as CT-or-NG-related PID (chlamydial PID (N74.4 + A56.1) or gonococcal PID (N74.3 + A54.2), *acute PID* [N70.0, N71.0, N73.0), *unspecified PID* (N70.9, N71.9, N73.2, N73.5, N73.8, N73.9), or, *chronic PID* (N70.1, N71.1, N73.1, N73.4).

Data sources for population and live birth denominators

Population denominator data were obtained at residential postcode level and included estimated residential population by year and age,[7] remoteness,[8] and level of socio-economic disadvantage based on the index of relative socio-economic disadvantage[9] of residential postcode. As in another Australian study, we obtained the number of live births for the three states by maternal age and year (2009-2014), these data were not at postcode level.[10] Other pregnancy outcome data (e.g. stillbirths, abortion) are not routinely available so we could not construct a denominator of all conceptions.

Sensitivity analyses

Two sensitivity analyses were undertaken to examine the robustness of our results. The first used linear splines to model the association for changes in PID and EP rates over time with knots specified at two year intervals, rather than assuming a linear relationship. The second repeated our univariable and multivariable analysis of PID and EP population rates by year, omitting postcodes recoded to neighbouring postcodes.

RESULTS

We show the annual number of diagnoses of PID and EP by diagnosis code in hospital admissions and ED presentations in supplementary table 2 and PID and EP rates per 100 000 women with 95% confidence intervals are shown in supplementary table 3.

Results for the linear splines sensitivity analysis are shown in supplementary table 4. The rate of change for population rates of PID and EP did not alter during the overall study period. The rate of change for EP rates among births in EDs during 2011 to 2012 was higher than the rate of change during 2009 to 2010.

Supplementary table 1: Data sources and description

Datatype	Source	Coverage	Description
Hospital admission	• Victorian Admitted Episodes Dataset • NSW Admitted Patient Data Collection • Queensland Hospital Admitted Patient Data Collection	All **public** and **private** hospitals in the Australian states of Victoria, NSW and Queensland are required to report the principal cause of hospitalisation (and other diagnoses) for each admitted episode of care ending in discharge, transfer or death. Number of hospitals providing admissions data (2009-14) • 2009: N=973 [public (n=533), private (n=440)] • 2014: N=998 [public (n=532), private (n=466)]	• Line listed de-identified demographic, clinical and administrative data for all admitted episodes of patient care • Core data items: age-group, year, patient residential postcode, principal diagnosis code *(ICD10-AM)*, other diagnoses code/s (number varied between jurisdictions) • Diagnoses coded by clinical coders.
Emergency department	• Victorian Emergency Minimum Dataset • NSW Emergency Department Data Collection • Queensland Emergency Department Information system	• **Public hospitals** with a designated emergency department. • Data inclusion limited to hospitals during 2009-2014: i) providing data annually ii) with <50% variation in the number of ED presentations iii) ≥ 75% completeness of diagnosis codes OR iv) >10000 annual presentations & <75% completeness. Number of hospitals providing data to emergency datasets (2009-14) 2010-11 n: Hospitals reporting data 151; Hospitals excluded 6; **Total hospitals included: 145** 2013-14 n: Hospitals reporting data 247; Hospitals excluded 102; **Total hospitals included: 145**	• Line listed de-identified demographic, clinical and administrative data for emergency department presentations. • Core data items: age-group, year, patient residential postcode, principal diagnosis code *(ICD10-AM, ICD9-CM, SNOMED)*, departure status (admitted, care complete in emergency) • Diagnoses coded by clinicians. • Other diagnosis code not provided by all jurisdictions.
Population denominator	Australian Bureau of Statistics	• Estimated residential population (2009-14) • Australian Statistical Geography Standard area classification • IRSD: a summary measure of variables derived from the Australian census indicating relative disadvantage of an area (e.g. proportion of low income households, persons unemployed, disability, manual laborers, low education, single parent families)	• Number of residents by postcode, age, year • Remoteness of residential postcode: metropolitan, inner-regional, outer-regional or remote • Deciles of relative disadvantage of postal area for Australia
Birth denominator	Australian Bureau of Statistics	• Number of live births (2009-14)	• Number of live births by maternal age, year for the states of Victoria, NSW, Queensland

Abbreviations: NSW: New South Wales; ICD10-AM: International Classification of Diseases, 10th Revision Australian Modification; ID9-CM: International Classification of Diseases, 9th Revision; SNOMED: Systematized Nomenclature of Medicine; IRSD: Index of Relative Socioeconomic Disadvantage

Supplementary table 2: Number of principal diagnoses of pelvic inflammatory disease and ectopic pregnancy by diagnosis code and year in: (A) public and private hospital admissions, and, (B) presentations to public hospital emergency departments that were included in the study (n=145)

A) PUBLIC and PRIVATE HOSPITAL ADMISSIONs ICD-10 code and description		2009 n (%)	2010 n (%)	2011 n (%)	2012 n (%)	2013 n (%)	2014 n (%)	Total n (%)
Pelvic inflammatory disease								
N70	**Salpingitis and oophoritis**							
N70.0	Acute salpingitis and oophoritis	25 (1.2)	39 (1.7)	45 (1.8)	47 (1.9)	43 (1.7)	40 (1.7)	239 (1.7)
N70.1	Chronic salpingitis and oophoritis	358 (16.7)	334 (14.4)	365 (14.5)	347 (14.3)	394 (15.8)	326 (13.7)	2,124 (14.9)
N70.9	Salpingitis and oophoritis, unspecified	155 (7.2)	177 (7.7)	190 (7.6)	183 (7.5)	172 (6.9)	172 (7.2)	1,049 (7.4)
N71	**Inflammatory disease of uterus, except cervix**							
N71.0	Acute inflammatory disease of uterus	28 (1.3)	33 (1.4)	23 (0.9)	18 (0.7)	25 (1.0)	34 (1.4)	161 (1.1)
N71.1	Chronic inflammatory disease of uterus	161 (7.5)	156 (6.7)	135 (5.4)	138 (5.7)	151 (6.0)	139 (5.9)	880 (6.2)
N71.9	Inflammatory disease of uterus, unspecified	217 (10.1)	211 (9.1)	256 (10.2)	234 (9.6)	257(10.3)	231 (9.7)	1,406 (9.9)
N73	**Other female pelvic inflammatory diseases**							
N73.0	Acute parametritis and pelvic cellulitis	62 (2.9)	61 (2.6)	101 (4.0)	80 (3.3)	78 (3.1)	72 (3.0)	454 (3.2)
N73.1	Chronic parametritis and pelvic cellulitis	36 (1.7)	42 (1.8)	35 (1.4)	37 (1.5)	33 (1.3)	24 (1.0)	207 (1.5)
N73.2	Unspecified parametritis and pelvic cellulitis	1 (0.1)	1 (0.0)	3 (0.1)	2 (0.1)	3 (0.1)	0 (0.0)	10 (0.1)
N73.3	Female acute pelvic peritonitis	9 (0.4)	7 (0.3)	7 (0.3)	6 (0.3)	6 (0.2)	6 (0.3)	41 (0.3)
N73.4	Female chronic pelvic peritonitis	2 (0.1)	3 (0.1)	2 (0.1)	1 (0.0)	2 (0.1)	0 (0.0)	10 (0.1)
N73.5	Female pelvic peritonitis, unspecified	9 (0.4)	21 (0.9)	14 (0.6)	12 (0.5)	8 (0.3)	8 (0.3)	72 (0.5)
N73.8	Other specified female pelvic inflammatory diseases	18 (0.8)	24 (1.0)	20 (0.8)	18 (0.7)	21 (0.8)	21 (0.9)	122 (0.9)
N73.9	Female pelvic inflammatory disease, unspecified	979 (45.7)	1,079 (46.6)	1,191 (47.5)	1,165 (48.0)	1,152 (46.0)	1,160 (48.8)	6,726 (47.1)
N74.3	Female gonococcal PID (A54.2 +)	2 (0.1)	0 (0.0)	1 (0.0)	5 (0.2)	1 (0.0)	1 (0.0)	10 (0.1)
N74.4	Female chlamydial PID (A56.1 +)	79 (3.7)	126 (5.5)	122 (4.9)	136 (5.6)	156 (6.2)	141(5.9)	760 (5.3)
	Total PID cases in admissions	**2,141 (100)**	**2,314 (100)**	**2,510 (100)**	**2,429 (100)**	**2,502 (100)**	**2,375 (100)**	**14,271 (100)**
Ectopic pregnancy								
O00	**Ectopic pregnancy**							
O00.0	Abdominal pregnancy	8 (0.2)	16 (0.4)	15 (0.4)	23 (0.6)	21 (0.5)	19 (0.5)	102 (0.4)
O00.1	Tubal pregnancy	2,708 (70.0)	2,693 (71.5)	2,773 (69.7)	2,692 (70.1)	2,796 (68.7)	2,809 (69.4)	16,471 (69.9)
O00.2	Ovarian pregnancy	88 (2.3)	70 (1.9)	99 (2.5)	71 (1.9)	110 (2.7)	87 (2.2)	525 (2.2)

O00.8	Other ectopic pregnancy	227 (5.9)	230 (6.1)	219 (5.5)	239 (6.2)	266 (6.5)	262 (6.5)	1,443 (6.1)
O00.9	Ectopic pregnancy, unspecified	839 (21.7)	759 (20.1)	875 (22.0)	816 (21.2)	879 (21.6)	870 (21.5)	5,038 (21.4)
	Total ectopic pregnancy cases in admissions	**3,870 (100)**	**3,768 (100)**	**3,981 (100)**	**3,841 (100)**	**4,072 (100)**	**4,047 (100)**	**23,579 (100)**
B)	**EMERGENCY DEPARTMENT PRESENTATIONS**							
Pelvic inflammatory disease*								
N70	**Salpingitis and oophoritis**							
N70.0	Acute salpingitis and oophoritis	1 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	1 (0.0)	1 (0.0)	5 (0.0)
N70.9	Salpingitis and oophoritis, unspecified	3 (0.1)	1 (0.0)	1 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	6 (0.0)
N71	**Inflammatory disease of uterus, except cervix**							
N71.0	Acute inflammatory disease of uterus	111 (4.3)	134 (4.5)	193 (5.6)	236 (6.1)	224 (5.5)	190 (5.2)	1088 (5.3)
N71.1	Chronic inflammatory disease of uterus	1 (0.0)	14 (0.5)	15 (0.4)	11 (0.3)	0 (0.0)	0 (0.0	41 (0.2)
N71.9	Inflammatory disease of uterus, unspecified	585 (22.8)	680 (22.9)	951 (27.6)	1178 (30.7)	1285 (31.6)	1304 (35.8)	5983 (29.2)
N73	**Other female pelvic inflammatory diseases**							
N73.0	Acute parametritis and pelvic cellulitis	47 (1.8)	33 (1.1)	23 (0.7)	8 (0.2)	12 (0.3)	7 (0.2)	130 (0.6)
N73.9	Female pelvic inflammatory disease, unspecified	1,814 (70.7)	2,097 (70.6)	2,248(65.4)	2,401 (62.6)	2,545 (62.6)	2,140 (58.8)	13245 (64.5)
N74.4	Female chlamydial PID (A56.1+)	4 (0.2)	10 (0.3)	7 (0.2)	3 (0.1)	0 (0.0)	0 (0.0)	24 (0.1)
	Total PID cases in emergency	**2566 (100)**	**2971 (100)**	**3438 (100)**	**3838 (100)**	**4067 (100)**	**3642 (100)**	**20522 (100)**
Ectopic pregnancy†								
O00	Ectopic pregnancy							
O00.1	Tubal pregnancy	488 (16.4)	481 (16.9)	497 (16.6)	517 (15.2)	480 (13.5)	484 (13.3)	2947 (15.2)
O00.8	Other ectopic pregnancy	55 (1.8)	66 (2.3)	85 (2.8)	60 (1.8)	14 (0.4)	7 (0.2)	287 (1.5)
O00.9	Ectopic pregnancy, unspecified	2,431 (81.7)	2,293 (80.7)	2,414 (80.6)	2,817 (83.0)	3,055 (86.1)	3,138 (86.5)	16148 (83.3)
	Total ectopic pregnancy cases in emergency	**2974 (100)**	**2840 (100)**	**2996 (100)**	**3394 (100)**	**3549 (100)**	**3629 (100)**	**19382 (100)**

*** Concordant ICD10, ICD9, SNOMED codes for pelvic inflammatory disease:** N70.0 (614.0, 155969007); N70.1 (614.1, 155970008); N70.9 (614.2, 155971007, 155968004); N71.0 (615.0, 12308003, 15597200, 237037006); N71.1 (615.1, 155974004, 237044002); N71.9 (615.9; N73.0: 614.3); N73.1 (614.4; N73.8: 614.8); N73.9 (614.9, 139049001, 155967009, 155986001, 161793004, 198130006); N74.4 (188463006, 198176005, 237043008, 237084006, 189312004, 367504009). There were no emergency PID cases with N70.1, N73.1, N73.2, N73.3, N73.4, N73.5, N73.8, N74.3 ICD10 codes.

†Concordant ICD10, ICD9, SNOMED codes for ectopic pregnancy: O00.1 (633.1, 370382007, 387615001, 387617009, 149989008, 149990004, 156082006); O00.2 (633.2, 149988000); O00.8 (633.8, 172001, 14721006, 17433009, 8670900, 88144003); O00.9 (633.9, 139019003, 34801009, 15608003, 156083001, 82688001). There were no emergency ectopic pregnancy cases with O00.1, O00.2 codes.

Supplementary table 3: Annual PID and EP rates per 100 000 women aged 15 to 44 years, 2009 to 2014

		2009	2010	2011	2012	2013	2014
		Rate (95% CI)	Rate (95% CI)	Rate (95% CI)	Rate (95% CI)	Rate (95% CI)	Rate (95% CI)
Pelvic inflammatory disease							
Hospital admission rates	Total	60.6 (58.0-63.2)	64.7 (62.1-67.4)	69.5 (66.8-72.3)	66.4 (63.8-69.1)	67.5 (64.9-70.2)	63.3 (60.8-65.9)
	Admitted from ED	34.9 (33.0-36.9)	39.2 (37.1-41.3)	43.9 (41.8-46.1)	43.0 (40.9-45.2)	45.0 (42.9-47.2)	43.0 (40.9-45.1)
ED presentation rates	Total	72.6 (69.8-75.5)	83.0 (80.1-86.1)	95.2 (92.1-98.4)	104.9 (101.6-108.2)	109.7 (106.3-113.1)	97.0 (93.9-100.2)
	Admitted to hospital	21.1 (19.6-22.7)	23.4 (21.8-25.0)	29.2 (27.5-31.0)	32.0 (30.2-33.9)	37.1 (35.1-39.1)	34.6 (32.7-36.5)
	Discharged from ED	51.5 (49.2-53.9)	59.6 (57.1-62.2)	66.0 (63.4-68.7)	72.8 (70.1-75.7)	72.6 (70.0-75.4)	62.4 (59.9-65.0)
Ectopic pregnancy							
Hospital admission rates	Total	109.5 (106.1-113.0)	105.3 (102.0-108.7)	110.2 (106.9-113.7)	105.0 (101.7-108.3)	109.8 (106.5-113.2)	107.8 (104.5-111.2)
	Admitted from ED	77.7 (74.8-80.6)	73.9 (71.1-76.8)	77.5 (74.6-80.4)	76.9 (74.1-79.8)	80.6 (77.7-83.5)	79.5 (76.7-82.4)
ED presentation rates	Total	84.1 (81.1-87.2)	79.4 (76.5-82.3)	83.0 (80.0-86.0)	92.7 (89.6-95.9)	95.7 (92.6-98.9)	96.7 (93.6-99.9)
	Admitted to hospital	65.8 (63.1-68.5)	62.4 (59.8-65.0)	65.5 (62.9-68.2)	72.6 (69.9-75.4)	75.5 (72.7-78.4)	74.2 (71.5-77.0)
	Discharged from ED	18.4 (17.0-19.8)	17.0 (15.6-18.4)	17.5 (16.1-18.9)	20.1 (18.7-21.7)	20.2 (18.9-21.7)	22.5 (21.0-24.1)

Abbreviations: 95% CI, 95% confidence interval; ED, emergency department.

Supplementary table 4: Rate of change by time-period for hospital admission and emergency department presentation rates of pelvic inflammatory disease and ectopic pregnancy

	Pelvic inflammatory disease			**Ectopic Pregnancy – population rates**			**Ectopic Pregnancy – live birth rates**		
	All admissions	All-ED	Non-admitted ED	All admissions	All-ED	Non-admitted ED	All admissions	All-ED	Non-admitted ED
	Coef* (95% CI)	Coef (95% CI)	Coef (95% CI)	Coef (95% CI)	Coef (95% CI)	Coef (95% CI)	Coef (95% CI)	Coef (95% CI)	Coef (95% CI)
Time-period									
2009 to 2010	5.3 (-9.7, 20.3)	10.4 (-19.0, 39.7)	7.9 (-9.2, 24.8)	-2.6 (-21.9, 16.7)	-5.9 (-17.4, 5.7)	-1.7 (-6.5, 3.1)	-0.2 (-3.8, 3.5)	-0.7 (-1.7, 0.3)	-0.2 (-1.0, 0.5)
2011 to 2012	1.2 (-6.3, 8.7)	12.4 (-2.3, 27.0)	7.5 (-1.0, 16.0)	0.3 (-9.4, 9.9)	6.9 (1.2, 12.7)	1.4 (-1.0, 3.8)	0.1 (-1.7, 1.9)	1.1 (0.6, 1.6) †	0.2 (-0.1, 0.6)
2013 to 2014	-2.2 (-9.7, 5.3)	-3.9 (-18.6, 10.8)	-5.0 (-13.5, 3.5)	0.6 (-9.0, 10.3)	2.5 (-3.3, 8.3)	1.31 (-1.1, 3.7)	0.5 (-1.3, 2.3)	0.8 (0.3, 1.2)	0.3 (-0.1, 0.7)

Abbreviations: ED, emergency department; Coef, coefficient; 95% CI, 95% confidence interval

* Coef represents the rate of change for each two year time-period

† The rate of change for EP in the ED during 2011 to 2012 was higher than the rate of change during 2009 to 2010 (change in slope (95% CI): **1.8 (0.5, 3.1))**

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